Micrograms of imipenem or cilastatin per milligram = \frac{A_u \times P_s \times d}{A_s \times 1000 \times W_s}

where:
- \(A_u\) = Area of the imipenem or cilastatin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the imipenem or cilastatin peak in the chromatogram of the imipenem or cilastatin acid working standard;
- \(P_s\) = Anhydrous imipenem or cilastatin activity in the respective working standards solutions in micrograms per milliliter;
- \(d\) = Dilution factor for the 10 samples; and
- \(W_s\) = Net contents of 10 containers in grams (gross weight of 10 containers in grams ± tare weight of 10 containers in grams).

(b) Calculate the imipenem or cilastatin content of the container as follows:

Milligrams of imipenem or cilastatin per container = \frac{A_u \times P_s \times d}{A_s \times 1000}

where:
- \(A_u\) = Area of the imipenem or cilastatin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the imipenem or cilastatin peak in the chromatogram of the imipenem or cilastatin working standard;
- \(P_s\) = Anhydrous imipenem or cilastatin activity in the imipenem or cilastatin working standard solution in micrograms per milliliter; and
- \(d\) = Dilution factor of the sample.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(a) of this chapter, using a solution containing 5.0 milligrams of imipenem per milliliter except inject 10 milliliters per kilogram of rabbit weight.

(4) Loss on drying. Proceed as directed in §436.200(a) of this chapter.

(5) pH. Proceed as directed in §436.202 of this chapter.

Subpart A—Bulk Drugs

§ 442.4 Cefaclor monohydrate.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefaclor monohydrate is the monohydrate form of \(\text{(6}_R, 7_R)-7-[\text{(R}_2-2\text{-amino-2-phenylacetamido}-3\text{-chloro-8-oxo-5-thia-1-azabicyclo}\left[4.2.0\right]\text{-2-carboxylic acid}}\). It is so purified and dried that:

(i) Its potency is not less than 860 micrograms and not more than 1,050 micrograms of cefaclor per milligram on an "as is" basis.

(ii) Its moisture content is not less than 3.0 percent and not more than 8.0 percent.

(iii) Its pH in an aqueous suspension containing 25 milligrams per milliliter is not less than 3.0 and not more than 4.5.

(iv) It gives a positive identity test.

(v) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of §431.20 of this chapter.

(b) Requests for certification; samples. In addition to complying with the requirements of §432.1 of this chapter, each such request shall contain:

§ 442.107 Cefadroxil hemihydrate capsules.
§ 442.107a Cefadroxil hemihydrate tablets.
§ 442.115 Cefixime trihydrate oral dosage forms.
§ 442.115a Cefixime trihydrate for oral suspension.
§ 442.115b Cefixime trihydrate tablets.
§ 442.115c Cefixime trihydrate for oral suspension.
§ 442.121 Cephaloglycin dihydrate oral dosage forms.
§ 442.121a Cephaloglycin dihydrate capsules.
§ 442.121b Cephaloglycin dihydrate for oral suspension.
§ 442.127 Cephalexin monohydrate oral dosage forms.
§ 442.127a Cephalexin monohydrate tablets.
§ 442.127b Cephalexin monohydrate capsules.
§ 442.127c Cephalexin monohydrate for oral suspension.
§ 442.128 Cephalexin hydrochloride monohydrate tablets.
§ 442.140 Cephradine for oral suspension.
§ 442.140a Cephradine for injection.
§ 442.140b Sterile cephradine.
§ 442.141 Cephradine dihydrate capsules.
§ 442.141a Cephradine dihydrate for oral suspension.
§ 442.141b Cephradine dihydrate tablets.
§ 442.141c Cephradine for oral suspension.
§ 442.154 Cefpodoxime proxetil oral dosage forms.
§ 442.154a Cefpodoxime proxetil tablets.
§ 442.154b Cefpodoxime proxetil granules for oral suspension.
§ 442.180 Cefprozil oral dosage forms.
§ 442.180a Cefprozil tablets.
§ 442.180b Cefprozil for oral suspension.
§ 442.180c Cefprozil oral dosage forms.

VerDate 17<Jul>96 11:55 Jul 29, 1996 Jkt 167069 PO 00000 Frm 00596 Fmt 8010 Sfmt 8010 C:\CFR\21V5.001 pfrm13
(i) Results of tests and assays on the batch for potency, moisture, pH, identity, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to obtain a stock solution containing 1 milligram of cefaclor per milliliter (estimated). Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 5.0 micrograms of cefaclor per milliliter (estimated).

(ii) Hydroxylamine colorimetric assay. Proceed as directed in § 442.40(b)(1)(ii) of this chapter, except prepare the working standard and sample solutions and calculate the cefaclor content as follows:

(a) Preparation of working standard solution. Dissolve and dilute an accurately weighed portion of the cefaclor working standard in sufficient 0.1M potassium phosphate buffer, pH 4.5 (as described in § 436.101(a)(4) of this chapter) to obtain a concentration of 1 milligram of cefaclor per milliliter.

(b) Preparation of sample solution. Dissolve an accurately weighed portion of the sample in sufficient 0.1M potassium phosphate buffer, pH 4.5 (as described in § 436.101(a)(4) of this chapter) to obtain a concentration of 1 milligram of cefaclor per milliliter.

(c) Calculations. Calculate the cefaclor content in micrograms per milligram as follows:

\[
\text{Micrograms of cefaclor per milligram} = \frac{A_u \times P_a}{A_s \times W_u}
\]

where:

\[A_u = \text{Absorbance of sample solution;}
\[P_a = \text{Potency of working standard solution in micrograms per milliliter;}
\[A_s = \text{Absorbance of working standard solution;}
\[W_u = \text{Milligrams of sample per milliliter of sample solution.}

(2) Moisture. Proceed as directed in § 436.201 of this chapter.

(3) pH. Proceed as directed in § 436.202 of this chapter, using an aqueous suspension containing 25 milligrams per milliliter.

(4) Identity. Proceed as directed in § 436.211 of this chapter, using the sample preparation described in paragraph (b)(2) of that section.

(5) Crystallinity. Proceed as directed in § 436.203(a) of this chapter.

[46 FR 3832, Jan. 16, 1981]
(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.
   (i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 20 micrograms of cefadroxil per milliliter (estimated).
   (ii) Hydroxylamine colorimetric assay for cefadroxil. Proceed as directed in §442.40(b)(1)(ii) of this chapter, except prepare the working standard and sample solutions and calculate the potency of the sample as follows:
      (a) Preparation of working standard solutions. Dissolve and dilute an accurately weighed portion of the cefadroxil working standard in sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to a concentration of 1 milligram of cefadroxil per milliliter.
      (b) Preparation of sample solutions. Dissolve an accurately weighed portion of the sample in sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to a concentration of 1 milligram of cefadroxil per milliliter.
      (c) Calculate the potency of the sample in micrograms per milligram as follows:
      \[
      \text{Micrograms of cefadroxil per milligram} = \frac{A_u \times P_u \times 100}{A_s \times W_s \times (100 - m)}
      \]
      where:
      \(A_u\) = Absorbance of sample solution;
      \(P_u\) = Potency of working standard solution in micrograms per milliliter;
      \(A_s\) = Absorbance of working standard solution;
      \(W_s\) = Milligrams of sample per milliliter of sample solution;
      \(m\) = Percent moisture in sample.
   (2) [Reserved]
   (3) Moisture. Proceed as directed in §436.201 of this chapter.
   (4) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 50 milligrams per milliliter.
   (5) Absorptivity. Determine the absorptance of the sample and standard solutions in the following manner: Dissolve accurately weighed portions of approximately 50 milligrams each of the sample and standard in 250 milliliters of distilled water. Transfer a 10-milliliter aliquot to a 100-milliliter volumetric flask and dilute to volume with distilled water. Using a suitable spectrophotometer and distilled water as the blank, determine the absorbance of each solution at 264 nanometers. Determine the percent absorptivity of the sample relative to the absorptivity of the standard using the following calculations:
   \[
   \text{Percent relative absorptivity} = \frac{\text{Absorbance of sample} \times \text{milligrams standard} \times \text{potency of standard in micrograms per milliliter} \times 100}{\text{Absorbance of standard} \times \text{milligrams sample} \times (100 - m)}
   \]
   where:
   \(m\) = Percent moisture in the samples.
   (6) Identity. Using the sample and working standard solutions prepared as described in paragraph (b)(5) of this section and a suitable spectrophotometer, record the ultraviolet spectrum from 220 to 340 nanometers. The spectrum of the sample compares qualitatively with that of the cefadroxil working standard.
   (7) Crystallinity. Proceed as directed in §436.203(a) of this chapter.

§ 442.7 Cefadroxil hemihydrate.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefadroxil hemihydrate is 7-[D-2-amino-2(p-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid hemihydrate. It is so purified and dried that:
   (i) Its potency is not less than 900 micrograms and not more than 1,050 micrograms of cefadroxil activity per milligram on an anhydrous basis.
§ 442.7

(ii) [Reserved]

(iii) Its moisture content is not less than 2.4 percent and not more than 4.5 percent.

(iv) The pH of an aqueous solution containing 50 milligrams per milliliter is not less than 4.0 and not more than 6.0.

(v) When calculated on an anhydrous basis, its absorptivity at 264 nanometers is not less than 95 percent and not more than 104 percent of that of the cefadroxil standard similarly treated and corrected for potency.

(vi) It passes the identity test.

(vii) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefadroxil potency, moisture, pH, absorptivity, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 20 micrograms of cefadroxil per milliliter (estimated).

(ii) Hydroxylamine colorimetric assay for cefadroxil. Proceed as directed in § 442.40(b)(1)(ii), except prepare the working standard and sample solutions and calculate the potency of the sample as follows:

(A) Preparation of working standard solutions. Dissolve and dilute an accurately weighed portion of the cefadroxil working standard in sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to a concentration of 1 milligram of cefadroxil per milliliter.

(B) Preparation of sample solutions. Dissolve an accurately weighed portion of the sample in sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to a concentration of 1 milligram of cefadroxil per milliliter (estimated).

(C) Calculations. Calculate the potency of the sample in micrograms per milligram as follows:

\[
\text{Micrograms of cefadroxil per milligram} = \frac{A_U \times P_a \times 100}{A_S \times W_U \times (100 - m)}
\]

where:

- \( A_U \) = Absorbance of sample solution;
- \( A_S \) = Absorbance of working standard solution;
- \( P_a \) = Potency of working standard solution in micrograms per milliliter;
- \( W_U \) = Milligrams of sample per milliliter of sample solution; and
- \( m \) = Percent moisture content of the sample.

(2) [Reserved]

(3) Moisture. Proceed as directed in § 436.201 of this chapter.

(4) pH. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 50 milligrams per milliliter.

(5) Absorptivity. Determine the absorbance of the sample and standard solutions in the following manner: Dissolve accurately weighed portions of approximately 50 milligrams each of the sample and standard in 250 milliliters of distilled water. Transfer a 10-milliliter aliquot to a 100-milliliter volumetric flask and dilute to volume with distilled water. Using a suitable spectrophotometer and distilled water as the blank, determine the absorbance of each solution at 264 nanometers. Determine the percent absorptivity of the sample relative to the absorptivity of the standard using the following calculations:

\[
\text{Percent relative absorptivity} = \frac{[\text{Absorbance of sample} \times \text{milligrams standard X potency of standard in micrograms per milligram} ]}{100}
\]
§ 442.9a Sterile cefamandole sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Sterile cefamandole sodium is 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(hydroxyphenylacetyl)amino]-3-[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate (ester). It is so purified and dried that:

(i) Its potency is not less than 810 micrograms and not more than 1,000 micrograms of cefamandole per milligram on an anhydrous basis.
(ii) It is sterile.
(iii) It is nonpyrogenic.
(iv) [Reserved]
(v) Its moisture content is not more than 2.0 percent.
(vi) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 3.5 and not more than 7.0.
(vii) It passes the identity test.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, and identity.
(ii) Samples required:

(a) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.
(b) For sterility testing: 20 packages, each containing equal portions of approximately 250 milligrams.

(b) Tests and methods of assay—(1) Potency. Use any of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.

(i) Hydroxylamine colorimetric assay. Proceed as directed in §442.40(b)(1)(ii) of this chapter, except use the cefamandole working standard.
(ii) Polarographic assay. Proceed as directed in §436.324 of this chapter.
(iii) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to obtain a concentration of 1 milligram of cefamandole per milliliter (estimated). Hydrolyze this solution in a 37°C constant temperature water bath for 60 minutes. Further dilute a portion of the hydrolyzed solution with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 2.0 micrograms of cefamandole per milliliter (estimated).

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cefamandole per milliliter.

(4) [Reserved]

(5) Moisture. Proceed as directed in §436.201 of this chapter.

(6) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(7) Identity. Proceed as directed in §436.211 of this chapter, using the mineral oil mull prepared as described in paragraph (b)(2) of that section.

[47 FR 32708, June 1, 1982, as amended at 50 FR 19919, May 13, 1985]
§ 442.10 Cefazolin.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefazolin is 3-[[5-(methyl-1,3,4-thiadiazol-2-yl)-thio]methyl]-7-[2-(1H-tetrazol-1-yl)acetamido]-3-cephem-4-carboxylic acid. It is so purified and dried that:

(i) Its cefazolin content is not less than 950 micrograms and not more than 1,030 micrograms of cefazolin per milligram calculated on an anhydrous basis.

(ii) Its moisture content is not more than 2 percent.

(iii) Its heavy metals content is not more than 20 parts per million.

(iv) It gives a positive identity test for cefazolin.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefazolin content, moisture, heavy metals, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: Nine packages, each containing approximately 500 milligrams, and one package containing approximately 5 grams.

(b) Tests and methods of assay—(1) Cefazolin content. Proceed as directed in §436.342 of this chapter.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) Heavy metals. Proceed as directed in §436.208 of this chapter.

(4) Identity. The high-pressure liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cefazolin working standard.

§ 442.11a Sterile cefazolin sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Sterile cefazolin sodium is the sodium salt of 3-[[5-(methyl-1,3,4-thiadiazol-2-yl)-thio]methyl]-7-[2-(1H-tetrazol-1-yl)acetamido]-3-cephem-4-carboxylic acid. It is so purified and dried that:

(i) Its cefazolin content is not less than 950 micrograms and not more than 1,030 micrograms of cefazolin per millgram calculated on an anhydrous basis.

(ii) Its moisture content is not more than 2 percent.

(iii) Its heavy metals content is not more than 20 parts per million.

(iv) It gives a positive identity test for cefazolin.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefazolin content, moisture, heavy metals, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: Nine packages, each containing approximately 500 milligrams, and one package containing approximately 5 grams.

(b) Tests and methods of assay—(1) Cefazolin content. Proceed as directed in §436.342 of this chapter.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) Heavy metals. Proceed as directed in §436.208 of this chapter.

(4) Identity. The high-pressure liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cefazolin working standard.
Food and Drug Administration, HHS

§ 442.11a

cephem - 4 - carboxylic acid. It is so purified and dried that:
(i) Its potency is not less than 850 micrograms and not more than 1050 micrograms of cefazolin per milligram calculated on an anhydrous basis. If it is packaged for dispensing, its cefazolin content is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of cefazolin that it is represented to contain.
(ii) It is sterile.
(iii) It is nonpyrogenic.
(iv) [Reserved]
(v) Its moisture content is not more than 6 percent.
(vi) Its pH in an aqueous solution containing 100 milligrams of cefazolin per milliliter is not less than 4.5 and not more than 6.0.
(vii) The specific rotation in a 0.1M sodium bicarbonate solution containing 50 milligrams of cefazolin per milliliter at 25° C. is \( \pm 17° \) calculated on an anhydrous basis.
(viii) It gives a positive identity test for cefazolin.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:
(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, specific rotation, and identity.
(ii) Samples required:
(a) If the batch is packaged for repackaging or for use in the manufacture of another drug:
(1) For all tests except sterility: 9 packages, each containing approximately 500 milligrams, and 1 package containing approximately 5 grams.
(2) For sterility testing: 20 packages, each containing approximately 300 milligrams.
(b) If the batch is packaged for dispensing:
(1) For all tests except sterility: A minimum of 15 immediate containers, except if each contains less than 1.0 gram, a minimum of 24 immediate containers.
(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Potency—(i) Sample preparation. Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration; also if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents. Dilute with sufficient solution 1 to give a stock solution of convenient concentration.
(ii) Assay procedure. Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.
(a) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 micrograms of cefazolin per milliliter (estimated).
(b) Hydroxylamine colorimetric assay. Proceed as directed in §436.205 of this chapter, preparing the working standard solution as follows: Dissolve an accurately weighed portion of approximately 30 milligrams of cefazolin working standard in 3 milliliters of 10 percent potassium phosphate buffer, pH 6.0 (solution 6), and further dilute with solution 1 to the final concentration.
(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cefazolin per milliliter.
(4) [Reserved]
(5) Moisture. Proceed as directed in §436.201 of this chapter.
(6) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams of cefazolin per milliliter.
(7) Specific rotation. Proceed as directed in §436.210 of this chapter, using a solution containing 50 milligrams of cefazolin per milliliter in 0.1M sodium bicarbonate and a polarimeter tube 1.0
decimeter in length. Calculate the specific rotation on an anhydrous basis.

(8) Identity. Using a 0.002 percent solution of the sample in 0.1M sodium bicarbonate solution and a suitable spectrophotometer, record the ultraviolet spectrum from 220 to 340 nanometers. The spectrum compares qualitatively to that of the cefazolin working standard similarly tested.

§ 442.12 Cefoperazone sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefoperazone sodium is the sodium salt of (6R, 7R)-7-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-p-hydroxyphenyl]acetamido]-3-[[1-methyl-1H-tetrazol-5-yl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. It is a white to off-white crystalline powder or a lyophilized powder. It is so purified and dried that:

(i) Its cefoperazone content is not less than 870 micrograms and not more than 1,015 micrograms of cefoperazone per milligram on an anhydrous basis.

(ii) Its moisture content is not more than 5.0 percent, except if it is the lyophilized powder, its moisture content is not more than 2.0 percent.

(iii) The pH of an aqueous solution containing 250 milligrams per milliliter is not less than 4.5 and not more than 6.5.

(iv) It passes the identity test if the retention times of the sample and working standard agree within ±3.0 percent.

(v) It is crystalline, except if it is the lyophilized powder.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefoperazone content, moisture, pH, identity, and crystallinity (if it is not the lyophilized powder).

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages containing approximately 500 milligrams.

(b) Tests and methods of assay—(1) Cefoperazone content. Proceed as directed in §436.338 of this chapter.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 250 milligrams per milliliter.

(4) Identity. From the high-performance liquid chromatograms of the sample and the cefoperazone working standard determined as directed in paragraph (b)(1) of this section, calculate the adjusted retention times of the cefoperazone in the sample and standard solutions as follows:

Adjusted retention time of cefoperazone = \(t \pm t_{a}\)

where:

\(t\) = Retention time measured from point of injection into the chromatograph until the maximum of the cefoperazone sample or working standard peak appears on the chromatogram; and

\(t_{a}\) = Retention time measured from point of injection into the chromatograph until the maximum of nonretarded solute appears in the chromatogram.

The sample and the cefoperazone working standard should have corresponding adjusted cefoperazone retention times within ±3.0 percent.

(5) Crystallinity. Proceed as directed in §436.203(a) of this chapter.

§ 442.12a Sterile cefoperazone sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Sterile cefoperazone sodium is the sodium salt of (6R, 7R)-7-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinocarboxamido)-2-p-hydroxyphenyl]acetamido]-3-[[1-methyl-1H-tetrazol-5-yl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. It is a white to off-white crystalline powder or it may be a lyophilized powder. It is so purified and dried that:

(i) If the cefoperazone sodium is not packaged for dispensing, its cefoperazone content is not less than 670 micrograms and not more than 1,015 micrograms of cefoperazone per milligram on an anhydrous basis. If the cefoperazone sodium is packaged for dispensing, its cefoperazone content is not less than 870 micrograms and not more than 1,015 micrograms of cefoperazone per milligram on an anhydrous basis. If the cefoperazone sodium is packaged for dispensing, its cefoperazone content is not less than 870 micrograms and not more than 1,015 micrograms of cefoperazone per milligram on an anhydrous basis.
dispensing, its cefoperazone content is not less than 870 micrograms and not more than 1,015 micrograms of cefoperazone per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefoperazone that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 2.0 percent.

(v) Its pH in an aqueous solution containing 250 milligrams per milliliter is not less than 4.5 and not more than 6.5.

(vi) It passes the identity test if the retention times of the sample and working standard agree within ±3 percent.

(vii) It is crystalline, except if it is the lyophilized powder, it is not crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples.

In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefoperazone content, sterility, pyrogens, moisture, pH, identity, and crystallinity (if it is not the lyophilized powder).

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) If the batch is packaged for repacking or for manufacturing use:

(1) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(2) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 10 immediate containers of the batch.

(2) For sterility testing: 20 immediate containers collected at regular intervals throughout each filling operation.

(3) Tests and methods of assay—(1) Cefoperazone content. Proceed as directed in §436.338 of this chapter.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 10 milligrams of cefoperazone per milliliter.

(4) Moisture. Proceed as directed in §436.201 of this chapter.

(5) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 250 milligrams per milliliter.

(6) Identity. From the high-pressure liquid chromatograms of the sample and the cefoperazone working standard determined as directed in paragraph (b)(1) of this section, calculate the adjusted retention times of the cefoperazone in the sample and standard solutions as follows:

\[
\text{Retention time of cefoperazone} = t_s - t_u
\]

where:

\( t_s \) = Retention time of working standard measured from point of injection into the chromatograph until the peak maximum appears on the chromatogram; and

\( t_u \) = Retention time of sample measured from point of injection into the chromatogram until the peak maximum appears on the chromatogram.

(7) Crystallinity. Proceed as directed in §436.203(a) of this chapter.


§ 442.13 Cefotaxime sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefotaxime sodium is the sodium salt of 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[(acetyloxy)methyl]-7-[[2-amino-4-thiazolyl]-(methoxyimino)acetyl]amino]-8-oxo-[6 alpha, 7 beta(Z)]]. It is so purified and dried that:

(i) Its potency is not less than 885 micrograms and not more than 1,002 micrograms of cefotaxime per milligram on an anhydrous basis.

(ii) Its moisture content is not more than 6.0 percent.

(iii) Its pH in an aqueous solution is not less than 4.5 and not more than 6.5.

(iv) It gives a positive identity test.
§ 442.13a Sterile cefotaxime sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefotaxime sodium is the sodium salt of 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[(acetyloxy)methyl]-7-[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-δβ(Z)-[6α-[[6α, 7β(R)]]. It is so purified and dried that:

(i) Its potency is not less than 855 micrograms and not more than 1,002 micrograms of cefotaxime per milligram on an anhydrous basis. If it is packaged for dispensing, its content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of cefotaxime that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 6.0 percent.

(b) Preparation of the working standard solution. Dissolve and dilute an accurately weighed portion of the cefotaxime working standard in sufficient distilled water to obtain a concentration of 1 milligram of cefotaxime per milliliter.

(c) Preparation of sample solution. Dissolve and dilute an accurately weighed portion of the sample in sufficient distilled water to obtain a concentration of 1 milligram of cefotaxime per milliliter (estimated).

(d) Calculation. Calculate the cefotaxime content in micrograms per milligram as follows:

\[
\text{Micrograms of cefotaxime per milligram} = \frac{A_s \times P_a}{A_w \times W_u}
\]

where:

\(A_s\) = Absorbance of sample solution;
\(P_a\) = Potency of working standard solution in micrograms per milliliter;
\(A_w\) = Absorbance of working standard solution; and
\(W_u\) = Milligrams of sample per milliliter of sample solution.

(2) Microbe. Proceed as directed in § 436.201 of this chapter.

(3) pH. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(4) Identity. Proceed as directed in § 436.323 of this chapter, except prepare spotting solutions as follows: Prepare solutions of the sample and working standard, each containing 1 milligram of cefotaxime per milliliter in distilled water.

(vi) Its pH in an aqueous solution is not less than 4.5 and not more than 6.5.
(vii) It gives a positive identity test.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:
(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, and identity.
(ii) Sample required:
(a) If the batch is packaged for repacking or for use as an ingredient in the manufacture of another drug:
(1) For all tests except sterility: 10 packages, each containing approximately 1 gram.
(2) For sterility testing: 20 packages, each containing approximately 1 gram.
(b) If the batch is packaged for dispensing:
(1) For all tests except sterility: A minimum of 10 immediate containers.
(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.
(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to obtain a stock solution of convenient concentration; also, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with solution 1 to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 2.0 micrograms of cefotaxime per milliliter (estimated).
(ii) Hydroxylamine colorimetric assay. Proceed as directed in §442.40(b)(1)(ii) of this chapter, except prepare the working standard and sample solutions and calculate the potency of the sample as follows:
(a) Preparation of the working standard solution. Dissolve and dilute an accurately weighed portion of the cefotaxime working standard in sufficient distilled water to obtain a concentration of 1 milligram of cefotaxime per milliliter.

(c) Calculations—(1) Calculate the cefotaxime content in micrograms per milligram as follows:

\[
\text{Micrograms of cefotaxime per milligram} = \frac{A_u \times P_a}{A_s \times W_u}
\]

where:
\(A_u\) = Absorbance of sample solution;
\(P_a\) = Potency of working standard solution in micrograms per milliliter;
\(A_s\) = Absorbance of working standard solution;
\(W_u\) = Milligrams of sample per milliliter of sample solution.

(2) Calculate the cefotaxime content of the single-dose vial as follows:

\[
\text{Milligrams of cefotaxime per single-dose vial} = \frac{A_u \times P_a \times d}{A_s \times 1,000}
\]

where:
\(A_u\) = Absorbance of sample solution;
\(P_a\) = Potency of working standard solution in micrograms per milliliter;
\(A_s\) = Absorbance of working standard solution;
\(d\) = Dilution factor of the sample.

(3) Calculate the cefotaxime content of the multiple-dose vial as follows:

\[
\text{Milligrams of cefotaxime per multiple-dose vial} = \frac{A_u \times P_a \times d}{A_s \times 1,000 \times n}
\]

where:
\(A_u\) = Absorbance of sample solution;
\(P_a\) = Potency of working standard solution in micrograms per milliliter;
Aₚ = Absorbance of working standard solution;
D = Dilution factor of the sample;
V = Volume of sample solution assayed.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(2) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cefotaxime per milliliter.

(4) [Reserved]

(5) Moisture. Proceed as directed in §436.201 of this chapter.

(6) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(7) Identity. Proceed as directed in §436.323 of this chapter, except prepare spotting solutions as follows: Prepare solutions of the sample and working standard, each containing 1 milligram of cefotaxime per milliliter in distilled water.

§ 442.14 Cefoxitin sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefoxitin sodium is the sodium salt of 3-(hydroxymethyl)-7α-methoxy-8-oxo-7-[2-(2-thienyl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid carbamate (ester). It is so purified and dried that:

(i) Its cefoxitin content is not less than 850 micrograms and not more than 1,000 micrograms of cefoxitin per milligram.

(ii) Its moisture content is not more than 2.0 percent.

(iii) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 4.2 and not more than 7.0.

(iv) It gives a positive identity test.

(v) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefoxitin content, moisture, pH, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) Tests and methods of assay—(1) Cefoxitin content. Proceed as directed in §436.347 of this chapter, preparing the working standard and sample solutions and calculating the cefoxitin content as follows:

(i) Working standard solution. Dissolve an accurately weighed portion of the cefoxitin working standard with water to obtain a solution containing 1 milligram of cefoxitin per milliliter.

(ii) Sample solution. Dissolve an accurately weighed portion of the sample with water to obtain a solution containing 1 milligram of cefoxitin per milliliter (estimated).

(iii) Calculations. Calculate the micrograms of cefoxitin per milligram of sample as follows:

\[ \text{Micrograms of cefoxitin per milligram} = \frac{A_u \times P_s}{A_s \times C_u} \]

where:

\( A_u \) = Area of the cefoxitin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

\( A_s \) = Area of the cefoxitin peak in the chromatogram of the cefoxitin working standard;

\( P_s \) = Cefoxitin activity in the cefoxitin working standard solution in micrograms per milliliter; and

\( C_u \) = Milligrams of sample per milliliter of sample solution (estimated).

(2) Moisture. Proceed as directed in §436.201 of this chapter, using the titration procedure described in paragraph (e)(1) of that section, except add about 25 milliliters of methanol in lieu of solvent A to a dry titrating vessel and proceed as directed in titration procedure 1.

(3) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(4) Identity. Proceed as directed in §436.326 of this chapter.
§ 442.14a Sterile cefoxitin sodium.

(a) Requirements for certification—

(1) Standards of identity, strength, quality, and purity. Cefoxitin sodium is the sodium salt of 3-(hydroxymethyl)-7α-methoxy-8-oxo-7-[2-(2-thienyl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid carbamate (ester). It is so purified and dried that:

(i) Its potency is not less than 850 micrograms and not more than 1,000 micrograms of cefoxitin per milligram. If it is packaged for dispensing, its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefoxitin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 2.0 percent.

(vi) Its pH in an aqueous solution is not less than 4.2 and not more than 7.0.

(vii) It gives a positive identity test.

(viii) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples.

In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, identity, and crystallinity.

(ii) Samples required:

(a) If the batch is packaged for repacking or for use as an ingredient in the manufacture of another drug:

(1) For all tests except sterility: 10 packages, each containing approximately 1 gram.

(2) For sterility testing: 20 packages, each containing approximately 1 gram.

(b) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—

(1) Potency. Proceed as directed in § 436.347 of this chapter, preparing the working standard and sample solutions and calculating the cefoxitin content as follows:

(i) Working standard solution. Dissolve an accurately weighed portion of the cefoxitin working standard with distilled water to obtain a solution containing 1 milligram of cefoxitin per milliliter (estimated); and also if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with distilled water to obtain a solution containing 1 milligram of cefoxitin per milliliter (estimated).

(ii) Sample solutions. Dissolve an accurately weighed portion of the sample with distilled water to obtain a solution containing 1 milligram of cefoxitin per milliliter (estimated); and also if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with distilled water to obtain a solution containing 1 milligram of cefoxitin per milliliter (estimated).

(iii) Calculations—

(a) Calculate the cefoxitin content in micrograms per milligram as follows:

\[
\text{Micrograms of cefoxitin per milligram} = \frac{A_u \times P_s}{A_j \times C_u}
\]

where:

- \(A_u\) = Area of the cefoxitin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_j\) = Area of the cefoxitin peak in the chromatogram of the cefoxitin working standard;
- \(P_s\) = Cefoxitin activity in the cefoxitin working standard solution in micrograms per milliliter; and
- \(C_u\) = Milligrams of sample per milliliter of sample solution (estimated).

(b) Calculate the cefoxitin content of the vial as follows:

\[
\text{Milligrams of cefoxitin per vial} = \frac{A_u \times P_j \times d}{A_j \times 1,000}
\]
§ 442.15 Cefixime trihydrate.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefixime trihydrate is the trihydrate form of \( \text{[6R-[6a, 7B(Z)]-7-} \)
\([\text{2-amino-4-thiazolyl}] \)\( \text{iminooacetyle} \)
\( \text{amino}-3\text{-ethenyl-8-oxo-5-thiazabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that: (i) Its potency is not less than 950 micrograms and not more than 1,030 micrograms of cefixime activity per milligram, on an anhydrous basis.}

(ii) Its moisture content is not less than 9.0 percent and not more than 12.0 percent.

(iii) The pH of an aqueous solution containing the equivalent of 0.7 milligram per milliliter is not less than 2.6 and not more than 4.1.

(iv) It is crystalline.

(v) The specific rotation in a 2.0 percent sodium bicarbonate solution containing 10.0 milligrams of cefixime per milliliter at 25 °C is between \(-75^\circ\) and \(-88^\circ\) calculated on an anhydrous basis.

(vi) It gives a positive identity test for cefixime.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cefixime per milliliter.

(4) [Reserved]

(5) Moisture. Proceed as directed in §436.201 of this chapter, using the titration procedure described in paragraph (e)(1) of that section, except add about 25 milliliters of methanol in lieu of solvent A to a dry titrating vessel and proceed as directed in titration procedure 1.

(6) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(7) Identity. Proceed as directed in §436.326 of this chapter, preparing the sample as follows: Prepare a solution containing about 2.5 milligrams of cefixime per milliliter in distilled water.

(8) Crystallinity. Proceed as directed in §436.203(a) of this chapter.

Filter the mobile phase through a suitable glass filter or equivalent which is capable of removing particulate contamination greater than 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(D) 0.1M Phosphate buffer, pH 7.0. Add 6.8 milliliters of concentrated phosphoric acid to 300 milliliters of water. Adjust the pH to 7.0 with 10N sodium hydroxide. Dilute to 1,000 milliliters with water.

(ii) Preparation of working standard, test and sample solutions—(A) Working standard solution. Dissolve an accurately weighed portion of the cefixime standard with sufficient 0.1M phosphate buffer, pH 7.0, to obtain a solution containing approximately 2 milligrams of cefixime activity per milliliter. Further dilute quantitatively to a final concentration of 0.2 milligram of cefixime activity per milliliter in 0.1M phosphate buffer, pH 7.0. Prepare the working standard solution just prior to its introduction into the chromatograph.

(B) System suitability test solution. Dissolve an accurately weighed portion of cefixime working standard in distilled water to obtain a solution containing approximately 1.0 milligram of cefixime activity per milliliter. Heat this solution at 95 °C (in an oil bath) for 45 minutes. This procedure allows the (E)-isomer of cefixime to be generated in situ. Prepare the test solution just prior to its introduction into the chromatograph.

(C) Sample solution. Accurately weigh approximately 100 milligrams of the sample into a 50-milliliter volumetric flask. Dilute to volume with 0.1M phosphate buffer, pH 7.0, to obtain a solution containing approximately 2 milligrams of cefixime activity per milliliter. Mix well. Immediately prior to chromatography, further dilute 10 milliliters of stock solution to 100 milliliters with 0.1M phosphate buffer, pH 7.0 to obtain a solution containing 0.2 milligram of cefixime activity per milliliter (estimated).

(iii) System suitability requirements—(A) Asymmetry factor. Calculate the asymmetry factor (A_s), measure data point that is 10 percent of the cefixime peak height from the baseline, as follows:

\[
A_s = \frac{a + b}{2a}
\]

where:
- \(a\) = Horizontal distance from point of ascent to point of maximum peak height; and
- \(b\) = Horizontal distance from the point of maximum peak height to point of descent.

The asymmetry factor (A_s) is satisfactory if it is not less than 0.85 and not more than 1.5.

(B) Efficiency of the column. From the number of theoretical plates (n) calculated as described in §436.216(c)(2) of this chapter calculate the reduced plate height (h_r) for the cefixime peak as follows:

\[
h_r = \frac{(L)(10,000)}{(n)(d_p)}
\]

where:
- \(L\) = Length of the column in centimeters;
- \(n\) = number of theoretical plates; and
- \(d_p\) = Average diameter of the particles in the column in micrometers.

The absolute efficiency (h_r) is satisfactory if it is not more than 15 for the cefixime peak.

(C) Resolution. The resolution (R) between the peak for cefixime and the peak for the (E)-isomer of cefixime (generated in situ) is not less than 1.1.

(D) Coefficient of variation (relative standard deviation). The coefficient of variation (S) in percent) of five replicate injections is satisfactory if not more than 2.0 percent.

(E) Capacity factor (k). Calculate the capacity factor (k) for cefixime as follows:

\[
k = \frac{t_r - t_m}{t_m}
\]

where:
- \(t_r\) = Retention time of solute; and
- \(t_m\) = Retention time of solvent or unretained substance, calculated as follows:

\[
t_m = \frac{(3.1416)(D^2)(L)(0.75)}{4F}
\]

where:
- \(D\) = Column diameter in centimeters;
- \(L\) = Column length in centimeters;
§ 442.16

0.75=Average total column porosity; and F=Flow rate in milliliters per minute.

The capacity factor (k) for cefixime is satisfactory if it is not less than 5 and not more than 11.

If the system suitability requirements have been met, then proceed as described in §436.216(b) of this chapter. Alternate chromatographic conditions are acceptable provided that the system suitability parameters are met. However, the sample preparation described in paragraph (b)(1)(ii)(C) of this section should not be changed.

(iv) Calculations. Calculate the micrograms of cefixime anhydrous free acid per milligram as follows:

\[
\text{Micrograms of cefixime per milligram} = \frac{A_s \times P_s \times 100}{A_u \times C_u \times (100 - m)}
\]

where:
- \( A_u \) = Area of the cefixime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \( A_s \) = Area of the cefixime peak in the chromatogram of the cefixime working standard;
- \( P_s \) = Cefixime activity in the cefixime working standard solution in micrograms per milliliter;
- \( C_u \) = Milligrams of sample per milliliter of sample solution; and
- \( m \) = Percent moisture content of the sample.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 5 milligrams of cefixime per milliliter.

(4) Crystallinity. Proceed as directed in §436.203(a) of this chapter.

(5) Specific rotation. Dissolve and dilute an accurately weighed sample with sufficient 2 percent sodium bicarbonate to obtain a concentration of approximately 10 milligrams of cefixime per milliliter. Proceed as directed in §436.210 of this chapter, using a 1.0-decimeter polarimeter tube. Calculate the specific rotation on the anhydrous basis.

(6) Identity. Proceed as directed in §436.211 of this chapter, using a potassium bromide disc containing 0.5 percent of cefixime. Dissolve 5 to 6 milligrams of cefixime in 2 milliliters of methanol. Triturate to insure solution.

Evaporate the solvent to dryness and using the dried sample, prepare the potassium bromide disc.

§ 442.16  Ceftazidime pentahydrate.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Ceftazidime pentahydrate is pyridinium, 1-[[7-[[2-amino-4-thiazolyl]-[1-carboxy-1-methyl]ethoxy]iminooacetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl, hydroxide, inner salt, [6α-[6α,7β(Z)]]-, pentahydrate. It is so purified and dried that:

(i) Its potency is not less than 950 micrograms and not more than 1,020 micrograms of ceftazidime activity per milligram on an anhydrous basis.

(ii) Its loss on drying is not less than 13.0 percent and not more than 15.0 percent.

(iii) The pH of an aqueous solution containing 5 milligrams of ceftazidime per milliliter is not less than 3.0 and not more than 4.0.

(iv) It is crystalline.

(v) It gives a positive identity test for ceftazidime.

(vi) Its high molecular weight polymer content is not more than 0.05 percent.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, loss on drying, pH, crystallinity, identity, and high molecular weight polymer content.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in §442.16a(b)(1).

(2) Loss on drying. Proceed as directed in §436.200(a) of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 5 milligrams of ceftazidime per milliliter.
(4) Crystallinity. Proceed as directed in §436.203(a) of this chapter.

(5) Identity. The high performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the ceftazidime working standard.

(6) High molecular weight polymer content. Proceed as directed in §442.16a(b)(8).

§ 442.16a Sterile ceftazidime pentahydrate.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Sterile ceftazidime pentahydrate is pyridinium, 1-[7-[[2-amino-4-thiazolyl][[(1-carboxy-1-methylene)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6α, 7β(Z)]]-, pentahydrate. It is so purified and dried that:

(i) Its potency is not less than 950 micrograms and not more than 1,020 micrograms of ceftazidime activity per milligram on an anhydrous basis.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its loss on drying is not less than 13.0 and not more than 15.0 percent.

(v) Its pH in an aqueous solution containing 5 milligrams of ceftazidime per milliliter is not less than 3.0 and not more than 4.0.

(vi) It is crystalline.

(vii) It gives a positive identity test for ceftazidime.

(viii) Its high molecular weight polymer content is not more than 0.05 percent.

(b) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(2) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, loss on drying, pH, crystallinity, identity, and high molecular weight polymer content.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(b) For sterility testing: One package containing approximately 6 grams of a composite sample.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in §436.256 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as hexyl, octyl, or octadecyl hydrocarbon bonded silicas, a flow rate of 2.0 milliliters per minute, and a known injection volume of 20 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) Reagents—(a) Phosphate buffer, pH 7.0. Dissolve 42.59 grams of sodium phosphate, dibasic anhydrous and 27.22 grams of potassium phosphate, monobasic, in water and dilute to 1,000 milliliters.

(b) Mobile phase. Mix 40 milliliters of acetonitrile and 200 milliliters of phosphate buffer, pH 7.0, and dilute to 2,000 milliliters with water. Filter the mobile phase through a suitable glass fiber filter or equivalent that is capable of removing particulate contamination to 1 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph pumping system.

(ii) Preparation of working standard and sample solutions—(a) Working standard solution. Accurately weigh ceftazidime working standard equivalent to approximately 100 milligrams of the ceftazidime activity into a 100-milliliter volumetric flask containing 10 milliliters of phosphate buffer, pH 7.0. Shake until dissolved. Dilute to volume with water to obtain a stock solution containing approximately 1,000 micrograms of ceftazidime activity per milliliter. Mix well. Immediately prior to chromatography, further dilute 5 milliliters of stock solution to 50 milliliters with water to obtain a solution containing 100 micrograms of ceftazidime activity per milliliter.

(b) Sample solution. Accurately weigh approximately 115 milligrams of the
§ 424.16a  21 CFR Ch. I (4-1-96 Edition)

sample into a 100-milliliter volumetric flask containing 10 milliliters of phosphate buffer, pH 7.0. Shake until dissolved. Dilute to volume with water to obtain a stock solution containing approximately 1,000 micrograms of ceftazidime per milliliter. Mix well immediately prior to chromatography, further dilute 5 milliliters of stock solution to 50 milliliters with water to obtain a solution containing 100 micrograms of ceftazidime activity per milliliter (estimated).

(iii) System suitability requirements—

(a) Tailing factor. The tailing factor (T) is satisfactory if it is not more than 1.5 at 5 percent of peak height.

(b) Efficiency of the column. The efficiency of the column (n) is satisfactory if it is greater than 1,500 theoretical plates.

(c) Resolution. The resolution (R) between the peak for ceftazidime and its nearest eluting impurity is satisfactory if it is not less than 2.0.

(d) Coefficient of variation. The coefficient of variation (S_u in percent) of five replicate injections is satisfactory if it is not more than 1.0 percent.

If the system suitability requirements have been met, then proceed as described in § 436.350(b) of this chapter. Alternate chromatographic conditions are acceptable provided reproducibility and resolution are provided comparable to the system. However, the sample preparation described in paragraph (e)(1)(ii)(b) of this section should not be changed.

(iv) Calculations. Calculate the micrograms of ceftazidime per milligram of sample as follows:

\[ \text{Micrograms of ceftazidime per milligram} = \frac{A_u \times P \times 100}{A_s \times C_s (100 - m)} \]

where:

- \( A_u \) = Area of the ceftazidime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \( A_s \) = Area of the ceftazidime peak in the chromatogram of the ceftazidime working standard;
- \( P \) = Ceftazidime activity in the ceftazidime working standard solution in micrograms per milliliter;
- \( C_s \) = Milligrams of sample per milliliter of sample solution; and

\( m \) = Percent loss on drying content of the sample.

(2) Sterility. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except dissolve the sample in approximately 200 milliliters of diluting fluid H.

(3) Pyrogens. Proceed as directed in § 436.32(i) of this chapter, using a solution containing 80 milligrams of ceftazidime per milliliter.

(4) Loss on drying. Proceed as directed in § 436.202(a) of this chapter.

(5) \( \text{pH} \). Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 5 milligrams of ceftazidime per milliliter.

(6) Crystallinity. Proceed as directed in § 436.203(a) of this chapter.

(7) Identity. The high-performance liquid chromatogram of the sample determined as directed in paragraph (b)(1)(ii)(b) of this section compares qualitatively to that of the ceftazidime working standard.

(8) High molecular weight polymer content. Proceed as directed in § 436.360 of this chapter, using a constant temperature between 20 and 25°C, an ultraviolet detection system operating at a wavelength of 235 nanometers, a column packed with a hydrophilic gel for gel permeation chromatography (such as Fractogel TSK HW-40(F), Merck) or equivalent, a flow rate of 1.0 milliliter per minute, and a known injection volume of 100 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) Reagents—(a) Mobile phase. Adjust a 0.1M solution of potassium phosphate, dibasic, to pH 7.0±0.1 with phosphoric acid.

(b) Blue dextran system suitability test solution. Prepare a solution in mobile phase containing 100 micrograms per milliliter of blue dextran (with a mean molecular weight of approximately 2,000,000).

(ii) Preparation of working standard and sample solutions—(a) Working standard solution. Accurately weigh high molecular weight polymer working standard equivalent to approximately 400 micrograms of high molecular weight polymer into a 100-milliliter volumetric flask and add 80 milliliters of
Food and Drug Administration, HHS § 442.17

mobile phase. Shake until dissolved and dilute to volume with mobile phase to obtain a solution containing approximately 4 micrograms of high molecular weight polymer per milliliter. Store the solution at ambient temperature and inject into the chromatograph within one hour of preparation.

(b) Sample solution. Accurately weigh approximately 400 milligrams of the sample into a 100-milliliter volumetric flask and add 80 milliliters of mobile phase. Shake until dissolved, dilute to volume with mobile phase, and immediately inject the solution into the liquid chromatograph.

(iii) System suitability requirements—
(a) Tailing factor. The tailing factor (T) is satisfactory if it is not more than 1.5 for blue dextran.
(b) Efficiency of the column. The efficiency of the column (n) is satisfactory if it is greater than 1,500 theoretical plates for blue dextran.
(c) Coefficient of variation. The coefficient of variation (S_R in percent) of five replicate injections of blue dextran is satisfactory if it is not more than 4 percent.

If the system suitability requirements have been met, then proceed as described in §436.360(b) of this chapter.

(iv) Calculations. Calculate the percent of high molecular weight polymer content as follows:

\[
\text{High molecular weight polymer content in percent} = \frac{H_u \times P_s \times 0.1}{H \times C_u}
\]

where:
- \(H_u\) = Height of the high molecular weight polymer peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(H\) = Mean height of the high molecular weight polymer peaks in the chromatograms of the high molecular weight polymer working standard;
- \(P_s\) = High molecular weight polymer content of the high molecular weight polymer working standard solution in micrograms per milliliter; and
- \(C_u\) = Milligrams of sample per milliliter of sample solution.

§ 442.17 Ceftizoxime sodium.

(a) Requirements for certification—
(1) Standards of identity, strength, quality, and purity. Ceftizoxime sodium is the sodium salt of \(\{6R,\{6\alpha, 7\beta\}\}]-7-[(2,3-dihydro-2-imino-4-thiazolyl)methoxyimino]oct-2-ene-2-carboxylic acid. It is so purified and dried that:
   (i) Its ceftizoxime content is not less than 850 micrograms and not more than 995 micrograms of ceftizoxime per milligram on an anhydrous basis.
   (ii) Its moisture content is not more than 8.5 percent.
   (iii) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 6.0 and not more than 8.0.
   (iv) It gives a positive identity test.
   (v) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:
   (i) Results of tests and assays on the batch for ceftizoxime content, moisture, pH, identity, and crystallinity.
   (ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams, and 1 package containing approximately 5 grams.

(b) Tests and methods of assay—
(1) Ceftizoxime content. Proceed as directed in §436.345 of this chapter, preparing the sample solution and calculating the ceftizoxime content as described in paragraphs (e)(1) and (g)(1), respectively, of that section.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(4) Identity. The high-pressure liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section, compares qualitatively to that of the ceftizoxime working standard.
§ 442.17a

(5) Crystallinity. Proceed as directed in §436.203(a) of this chapter.

§ 442.17a Sterile ceftizoxime sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Ceftizoxime sodium is the sodium salt of \([6\alpha, 7\beta(2)]\)-7-[(2,3-dihydro-2-imino-4-thiazoyl)\[(methoxyimino) acetyl]amino]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) If the ceftizoxime is not packaged for dispensing, its ceftizoxime content is not less than 850 micrograms and not more than 995 micrograms of ceftizoxime per milligram on an anhydrous basis. If the ceftizoxime is packaged for dispensing, its ceftizoxime content is not less than 850 micrograms and not more than 995 micrograms of ceftizoxime per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 115 percent of the number of milligrams of ceftizoxime that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 8.5 percent.

(v) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 6.0 and not more than 8.0.

(vi) It gives a positive identity test.

(vii) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(b) Requests for certification; samples. In addition to complying with the requirements of §432.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for ceftizoxime content, sterility, pyrogens, moisture, pH, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) If the batch is packaged for repacking or for use in the manufacture of another drug:

(1) For all tests except sterility: 10 packages, each containing at least 500 milligrams.

(2) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 10 immediate containers; or if each container contains less than 1 gram of ceftizoxime, a minimum of 20 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(c) Tests and methods of assay—(1) Ceftizoxime content. Proceed as directed in §436.345 of this chapter.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of ceftizoxime per milliliter.

(4) Moisture. Proceed as directed in §436.201 of this chapter.

(5) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(6) Identity. From the high-pressure liquid chromatograms of the sample and the ceftizoxime working standard determined as directed in paragraph (b)(1) of this section, calculate the adjusted retention times of the ceftizoxime in the sample and standard solutions as follows:

\[
\text{Adjusted retention time of ceftizoxime} = t - t_a
\]

where:

\( t \) = Retention time measured from point of injection into the chromatograph until the maximum of the ceftizoxime sample or working standard peak appears on the chromatogram; and

\( t_a \) = Retention time measured from point of injection into the chromatograph until the maximum of nonretarded solute appears in the chromatogram.

The sample and the ceftizoxime working standard should have corresponding adjusted ceftizoxime retention times.
§ 442.18 Cefuroxime sodium.

(a) Requirements for certification—

(1) Standards of identity, strength, quality, and purity. Cefuroxime sodium is the sodium salt of (6R, 7R)-3-carbamoyloxy-methyl-7-[(2Z)-2-(2-furyl)-2-methoxyiminoacetamido]cepha-3-em-4-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 855 micrograms and not more than 1,000 micrograms of cefuroxime activity per milligram on an anhydrous basis.

(ii) Its moisture content is not more than 3.5 percent.

(iii) The pH of an aqueous solution containing 100 milligrams of cefuroxime per milliliter is not less than 6.0 and not more than 8.5.

(iv) It gives a positive identity test for cefuroxime.

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 1 gram.

(b) Tests and methods of assay—

(1) Potency. Proceed as directed in §442.343.

(2) Moisture. Proceed as directed in §436.18a(b)(4) of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams of cefuroxime per milliliter.

(4) Identity. Proceed as directed in §442.18a(b)(6).


§ 442.18a Sterile cefuroxime sodium.

(a) Requirements for certification—

(1) Standards of identity, strength, quality, and purity. Cefuroxime sodium is the sodium salt of (6R, 7R)-3-carbamoyloxy-methyl-7-[(2Z)-2-(2-furyl)-2-methoxyiminoacetamido]cepha-3-em-4-carboxylic acid. It is so purified and dried that:

(i) If the cefuroxime is not packaged for dispensing, its cefuroxime content is not less than 855 micrograms and not more than 1,000 micrograms of cefuroxime per milligram on an anhydrous basis. If the cefuroxime is packaged for dispensing, its cefuroxime content is not less than 855 micrograms and not more than 1,000 micrograms of cefuroxime per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefuroxime that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 3.5 percent.

(v) Its pH in an aqueous solution is not less than 6.0 and not more than 8.5.

(vi) It gives a positive identity test.

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefuroxime content, sterility, pyrogens, moisture, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) If the batch is packaged for repacking or for use as an ingredient in the manufacture of another drug:

(1) For all tests except sterility: 10 packages, each containing approximately 1 gram.

(2) For sterility testing: 20 packages, each containing approximately 1 gram.

(b) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—

(1) Cefuroxime content. Proceed as directed in §436.343 of this chapter.
§ 442.19

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cefuroxime per milliliter.

(4) Moisture. Proceed as directed in §436.201 of this chapter, using the titration procedure described in paragraph (e)(1) of that section.

(5) pH. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(6) Identity. From the high-pressure liquid chromatograms of the sample and the cefuroxime working standard determined as directed in paragraph (b)(1) of this section, calculate the adjusted retention times of the cefuroxime in the sample and standard solutions as follows:

\[
\text{Adjusted retention time of cefuroxime} = t - t_a
\]

where:

- \(t\) = Retention time measured from point of injection into the chromatograph until the maximum of the cefuroxime sample or working standard peak appears on the chromatogram; and
- \(t_a\) = Retention time measured from point of injection into the chromatograph until the maximum of nonretarded solute appears in the chromatogram.

The sample and the cefuroxime working standard should have corresponding adjusted cefuroxime retention times.

(2) Cefuroxime axetil.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefuroxime axetil is an amorphous mixture of the diastereoisomers of 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[[(aminocarbonyl)oxy]methyl]-7-[[2-furanyl(methoxylimino)acetyl]amino]-8-oxo-1-(acetyloxy)ethyl ester, [6R-6 alpha, 7 beta (Z)]. It is so purified and dried that:

(i) Its potency is not less than 745 micrograms and not more than 875 micrograms of cefuroxime per milligram on an anhydrous basis. The ratio of isomer A to total isomer content is not less than 0.48 and not more than 0.55.

(ii) Its moisture content is not more than 1.5 percent.

(iii) It is amorphous and not crystalline.

(iv) It passes the identity test.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Request for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefuroxime potency, isomer A ratio, moisture, crystallinity, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in §436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 278 nanometers, a 25-centimeter by 4.6-millimeter column packed with methyl silane bonded silica 5 micrometers in particle size, a flow rate of 1 milliliter per minute, and a known injection volume of 10 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) Reagents—(A) 0.2M Ammonium phosphate solution. Transfer 23.0 grams of ammonium dihydrogen phosphate to a 1-liter volumetric flask. Dissolve and dilute to volume with distilled water. Mix well.

(B) Mobile phase. Transfer 380 milliliters of methanol to a 1-liter volumetric flask and dilute to volume with 0.2M ammonium phosphate solution.

(C) Internal standard solution. Prepare a solution containing 5.4 milligrams of acetanilide per milliliter in methanol.

(D) System suitability test solution. Mix 10.0 milliliters of a solution containing 1.2 milligrams of cefuroxime axetil working standard per milliliter in methanol with 5.0 milliliters of internal standard solution, 2.0 milliliters of a solution containing 0.3 milligram of an authentic sample of (RS)-1-acetoxyethyl-7-[[2-oxo-1-(acetyloxy)ethyl ester, [6R-6 alpha, 7 beta (Z)]]]. It is so purified and dried that:

(i) Its potency is not less than 745 micrograms and not more than 875 micrograms of cefuroxime per milligram on an anhydrous basis. The ratio of isomer A to total isomer content is not less than 0.48 and not more than 0.55.
§ 442.19

(yl)-2-methoxy-iminoacetamido]ceph-2-em-4-carboxylate (delta-2 isomers of cefuroxime axetil) per milliliter in methanol and 1.8 milliliters of methanol. Dilute to 50 milliliters with 0.2M ammonium phosphate solution.

(ii) Preparation of working standard and sample solutions—(A) Working standard solution. Dissolve approximately 30 milligrams of the cefuroxime axetil working standard, accurately weighed, in methanol and dilute to 25 milliliters with methanol. Immediately transfer 10.0 milliliters of the working standard solution to a 50-milliliter volumetric flask. Add 5.0 milliliters of internal standard solution and 3.8 milliliters of methanol, and dilute to volume with 0.2M ammonium phosphate solution to obtain a solution containing 0.2 milligram of cefuroxime activity per milliliter. Store the solution under refrigeration no more than 8 hours.

(B) Sample solution. Dissolve approximately 30 milligrams of the sample, accurately weighed, in methanol and dilute to 25 milliliters with methanol. Immediately transfer 10.0 milliliters of the sample solution to a 50-milliliter volumetric flask. Add 5.0 milliliters of internal standard solution and 3.8 milliliters of methanol, and dilute to volume with 0.2M ammonium phosphate solution to obtain a solution containing 0.2 milligram of cefuroxime activity per milliliter (estimated). Store the solution under refrigeration no more than 8 hours.

(iii) System suitability requirements—

(A) Tailing factor. The tailing factor \( T \) for isomer A if it is greater than 3,000 theoretical plates.

(B) Efficiency of the column. The efficiency of the column is satisfactory if it is not less than 1.5.

(C) Resolution. The resolution \( R \) between isomer A and isomer B of cefuroxime axetil is satisfactory if it is not less 1.5. If the system suitability requirements have been met, then proceed as directed in §436.216(b) of this chapter. Alternate chromatographic conditions are acceptable provided reproducibility and resolution are comparable to the system. However, the sample preparation described in paragraph (b)(1)(ii)(B) of this section should not be changed.

(iv) Calculations—

(A) Calculate the micrograms of cefuroxime per milligram of sample as follows:

\[
\text{Micrograms of cefuroxime per milligram} = \frac{R_u \times P_s \times 100}{R_s \times C_u \times (100 - m)}
\]

where:

- \( R_u \) = Sum of the peak height of the cefuroxime axetil sample isomer A and isomer B peaks/Peak height of the internal standard;
- \( R_s \) = Sum of the peak heights of the cefuroxime axetil working standard isomer A and isomer B peaks/Peak height of the internal standard;
- \( P_s \) = Cefuroxime activity in the cefuroxime axetil working standard solution in micrograms per milliliter;
- \( C_u \) = Milligrams of sample per milliliter of sample solution; and
- \( m \) = Percent moisture content of the sample.

(B) Calculate the ratio of isomer A to total isomer content as follows:

\[
\text{Ratio of isomer A to isomer content} = \frac{\text{Peak height of isomer A peak}}{\text{Peak height of isomer A peak} + \text{Peak height of isomer B peak}}
\]

(2) Moisture. Proceed as directed in §436.201 of this chapter, using the titration procedure described in paragraph (e)(1) of that section.

(3) Crystallinity. Proceed as directed in §436.203(a) of this chapter, except that the particles do not reveal the
§ 442.20a Sterile cefonicid sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Sterile cefonicid sodium is a white to off-white lyophilized powder. It is so purified and dried that:
   (i) If the cefonicid sodium is not packaged for dispensing, its cefonicid content is not less than 832 micrograms and not more than 970 micrograms of cefonicid per milligram on an anhydrous basis. If the cefonicid sodium is packaged for dispensing, its cefonicid content is not less than 832 micrograms and not more than 970 micrograms of cefonicid per milligram and each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefonicid that it is represented to contain.
   (ii) It is sterile.
   (iii) It is nonpyrogenic.
   (iv) Its moisture content is not more than 5.0 percent.
   (v) Its pH in an aqueous solution containing 50 milligrams per milliliter is not less than 3.5 and not more than 6.5.
   (vi) The specific rotation in a methanol solution containing 10 milligrams of cefonicid sodium per milliliter at 25° C is –42°±5°.
   (vii) It passes the identity test.

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 432.11 of this chapter, each such request shall contain:
   (i) Results of tests and assays on the batch for cefonicid content, sterility, pyrogens, moisture, pH, specific rotation, and identity.
   (ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) If the batch is packaged for repacking or for use as an ingredient in the manufacture of another drug:
   (1) For all tests except sterility: 10 packages, each containing at least 500 milligrams.
   (2) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.

(b) If the batch is packaged for dispensing:
   (1) For all tests except sterility: A minimum of 10 immediate containers.
   (2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Cefonicid content. Proceed as directed in § 436.350 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 254 nanometers, and a column packed with octadecyl silane bonded silica ranging from 3 to 30 micrometers in particle size. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:
   (i) Reagents—(a) 0.2M Ammonium phosphate solution. Transfer 23.0 grams of ammonium dihydrogen phosphate to a 1-liter volumetric flask. Dissolve and dilute to volume with distilled water. Mix well.
   (b) Mobile phase. Mix 0.2M ammonium phosphate solution:methyl alcohol:distilled water (1:2.5:16.5). Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) Working standard and sample solutions—(a) Preparation of working standard solution. Prepare the working standard solution fresh before injection by dissolving an accurately weighed portion of the cefonicid working standard with sufficient mobile phase as described in paragraph (b)(1)(i)(b) of this section to obtain a solution containing approximately 20 micrograms of cefonicid per milliliter.
   (b) Preparation of sample solutions—(1) Product not packaged for dispensing (micrograms of cefonicid per milligram). Dissolve an accurately weighed portion of the sample with sufficient mobile phase as described in paragraph
(b)(1)(i) of this section to obtain a concentration of approximately 20 micrograms of cefonicid per milliliter.  
(2) Product packaged for dispensing. Determine both micrograms of cefonicid per milligram of the sample and milligrams of cefonicid per container. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(ii)(b) of this section to obtain a concentration of approximately 20 micrograms of cefonicid per milliliter.

(i) Micrograms of cefonicid per milligram. Dissolve an accurately weighed portion of the sample suitable for chromatographic analysis in sufficient mobile phase as described in paragraph (b)(1)(i) of this section to obtain a concentration of approximately 20 micrograms of cefonicid per milliliter.

(ii) Milligrams of cefonicid per container. Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Further dilute an aliquot of the solution thus obtained with sufficient mobile phase to obtain a concentration of approximately 20 micrograms of cefonicid per milliliter.

(iii) System suitability requirements—
(a) Tailing factor. The tailing factor (T) is satisfactory if it is not more than 1.3 at 5 percent of peak height.

(b) Efficiency of the column. The efficiency of the column (n) is satisfactory if it is greater than 1,500 theoretical plates.

(c) Resolution factor. Prepare a resolution solution containing desacetyl cefonicid by heating a 200-microgram-per-milliliter solution of cefonicid working standard in mobile phase described in paragraph (b)(1)(i)(b) of this section, on a steam bath for 30 minutes. Inject a known volume between 10 and 20 microliters of the desacetyl cefonicid containing solution in the same manner as described for the standard solution. The resolution factor (R) between cefonicid and desacetyl cefonicid is satisfactory if it is not less than 1.1.

(d) Coefficient of variation. The coefficient of variation (Sv in percent) of five replicate injections is satisfactory if it is not more than 2.0 percent.

If the system suitability parameters have been met, then proceed as described in §436.350(b) of this chapter.

(iv) Calculations—(a) Calculate the micrograms of cefonicid per milligram of sample as follows:

\[
\text{Micrograms of cefonicid per milligram} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - m)}
\]

where:
- \(A_u\) = Area of the cefonicid peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the cefonicid peak in the chromatogram of the cefonicid working standard;
- \(P_s\) = Cefonicid activity in the cefonicid working standard solution in micrograms per milliliter;
- \(C_u\) = Milligrams of sample per milliliter of sample solution; and

\(m\) = Percent moisture content of the sample.

(b) Calculate the cefonicid content of the container as follows:

\[
\text{Milligrams of cefonicid per container} = \frac{A_u \times P_s \times d}{A_s \times 1,000}
\]

where:
- \(A_u\) = Area of the cefonicid peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the cefonicid peak in the chromatogram of the cefonicid working standard;
- \(P_s\) = Cefonicid activity in the cefonicid working standard solution in micrograms per milliliter; and

\(d\) = Dilution factor of the sample.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cefonicid per milliliter.

(4) Moisture. Proceed as directed in §436.201 of this chapter.

(5) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 50 milligrams per milliliter.
§ 442.21 Cephaloglycin dihydrate.

(a) Requirements for certification—

(1) Standards of identity, strength, quality, and purity. Cephaloglycin dihydrate is the dihydrate form of 7-(D-α-amino-phenylacetamido) cephalosporanic acid. It is a white to off-white powder. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms of cephaloglycin per milligram on an anhydrous basis.

(ii) Its moisture is not less than 8.2 and not more than 12 percent.

(iii) Its pH in an aqueous suspension containing 50 milligrams per milliliter is not less than 3.0 and not more than 5.5.

(iv) Its cephaloglycin content is not less than 95 and not more than 104 percent on an anhydrous basis.

(v) It gives a positive identity test for cephaloglycin dihydrate.

(vi) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5(b) of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, cephaloglycin content, identity, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 500 milligrams.

(b) Tests and methods of assay—

(1) Potency. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient sterile distilled water to give a stock solution of 100 micrograms of cephaloglycin per milliliter (estimated). Further dilute an aliquot of the stock solution with 0.1 M potassium phosphate buffer, pH 4.5 (solution 4), to the reference concentration of 10 micrograms of cephaloglycin per milliliter (estimated).

(2) [Reserved]

(3) Moisture. Proceed as directed in §436.201 of this chapter.

(4) pH. Proceed as directed in §436.202 of this chapter, using an aqueous suspension containing 50 milligrams per milliliter.

(5) Cephaloglycin content. Proceed as directed in §436.213 of this chapter, using the titration procedure described in paragraph (e)(2) of that section. Calculate the cephaloglycin content as follows:

$$\text{Percent cephaloglycin content} = \frac{(A-B) \times (\text{normality of perchloric acid reagent})}{(405.4) \times (100) \times (100)} \times \frac{1}{(\text{Weight of sample in milligrams}) \times (100-n)}$$

where:

- A = Milliliters of perchloric acid reagent used in titrating the sample;
- B = Milliliters of perchloric acid reagent used in titrating the blank;
- m = Percent moisture content of the sample.

(6) Identity. Proceed as directed in §436.211 of this chapter, using the 0.5-percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

(7) Crystallinity. Proceed as directed in §436.203(a) of this chapter.


§ 442.21 Specific rotation.

Dissolve and dilute an accurately weighed sample with sufficient methanol to obtain a concentration of approximately 10 milligrams of cefonicid sodium per milliliter. Proceed as directed in §436.210 of this chapter, using a 1.0-decimeter polarimeter tube. Calculate the specific rotation on an anhydrous basis.

(1) Identity. The high-performance liquid chromatogram of the sample, determined as directed in paragraph (b)(1) of this section, compares qualitatively to that of the cefonicid working standard.

§ 442.22a Sterile cefmenoxime hydrochloride.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefmenoxime hydrochloride is 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[2-amino-4-thiazolyl]methoxyimino]acetyl]amino]-3-[[1-methyl-1H-tetrazol-5-yl]thio]methyl]-8-oxo-, hydrochloride (2:1), [6\text{R}]-[6\alpha, 7\beta](Z)]-. It is so purified and dried that:

(i) Its cefmenoxime content is not less than 869 and not more than 1,015 micrograms of cefmenoxime per milligram on an anhydrous basis.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 1.5 percent.

(v) It passes the identity test.

(vi) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefmenoxime content, sterility, pyrogens, moisture, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(B) For sterility testing: 1 package containing approximately 6 grams of a composite sample.

(b) Tests and methods of assay—(1) Cefmenoxime content. Proceed as directed in § 436.363 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silicas, a flow rate not to exceed 2.0 milliliters per minute, and a known injection volume between 10 and 20 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) Reagents—(A) 0.1M Phosphate buffer solution, pH 6.8. Dissolve 6.4 grams of monobasic potassium phosphate and 18.9 grams of dibasic sodium phosphate in 750 milliliters of water. Adjust the pH to 6.8 with 1N sodium hydroxide and dilute to 1,000 milliliters.

(B) Internal standard solution. Dissolve and dilute 0.15 gram of phthalimide in methanol to 100 milliliters.

(C) Mobile phase. Mix water:acetonitrile:glacial acetic acid (50:10:1). Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) Preparation of working standard and sample solutions—(A) Working standard solution. Dissolve approximately 50 milligrams of the cefmenoxime working standard, accurately weighed, in 10 milliliters of 0.1M phosphate buffer solution, pH 6.8 and dilute to 50 milliliters with mobile phase. Transfer 4.0 milliliters of this solution to a 50-milliliter volumetric flask, add 20 milliliters of internal standard solution and dilute to volume with mobile phase to obtain a solution containing 80 micrograms of cefmenoxime per milliliter.

(B) Sample solution. Dissolve approximately 50 milligrams of cefmenoxime sample, accurately weighed, in 10 milliliters of 0.1M phosphate buffer solution, pH 6.8. Dilute to 50 milliliters with mobile phase. Transfer 4.0 milliliters of this solution to a 50-milliliter volumetric flask, add 20 milliliters of internal standard solution and dilute to volume with mobile phase.

(iii) System suitability requirements—(A) Tailing factor. The tailing factor (T) for the cefmenoxime peak is satisfactory if it is not more than 1.6 at 5 percent of peak height.

(B) Efficiency of the column. The efficiency of the column (n) is satisfactory if it is greater than 1,200 theoretical plates for the cefmenoxime peak.

(C) Resolution. The resolution (R) between the peak for cefmenoxime and phthalimide is satisfactory if it is not less than 2.3.

(D) Coefficient of variation. The coefficient of variation (S\text{R} in percent) of 5 replicate injections is satisfactory if it is not more than 2.0 percent. If the
§ 442.23a Sterile cephaloridine.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephaloridine is 7-[α-(2-thienyl)-acetamido]-3-(1-pyridyl-methyl)-3-cephem-4-carboxylic acid betaine. It is a white to off-white powder. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms of cephaloridine per milligram. If it is packaged for dispensing, its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cephaloridine that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its loss on drying is not more than 2.5 percent.

(v) Its pH in an aqueous solution containing 10 milligrams of cephaloridine per milliliter at 25°C is +48±4°.

(vi) It is crystalline.

(vii) The ultraviolet absorption spectrum between the wavelengths of 220 and 310 nanometers compares qualitatively to that of the cephaloridine working standard. The ratio of the absorbance of the maximum at the wavelength of 240 nanometers to that of the shoulder at 255 nanometers is not less than 1.05 and not more than 1.17.

(b) Labeling. It shall be labeled in accordance with the requirements prescribed by §432.5 of this chapter.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except in lieu of diluting fluid A use diluting fluid H.

(3) Pyrogens. Proceed as directed in §436.32(i) of this chapter, using a solution containing 60 milligrams per milliliter.

(4) Moisture. Proceed as directed in §436.20 of this chapter, using the sample preparation described in paragraph (d)(4) of that section and the titration procedure described in paragraph (e)(3) of that section, except:

(i) In lieu of 3 milliliters of anhydrous methanol solution, inject 20 milliliters of a formamide:methanol solution (2:1) into the container and shake to dissolve the contents (prior to use in preparation of the formamide:methanol solution, dry 500 grams of formamide over 20 grams of anhydrous sodium sulfate for 24 hours);

(ii) Rinse the syringe, needle, and immediate container with two separate 5-milliliter portions of anhydrous methanol; and

(iii) In §436.200 of this chapter, add a sufficient volume of the formamide:methanol solution (2:1) to cover the electrodes in the dry titrating vessel in lieu of 20 milliliters of solvent A before starting the titration.

[53 FR 13402, Apr. 25, 1988; 53 FR 19368, May 27, 1988]
(i) Results of tests and assays on the batch for potency, sterility, pyrogens, loss on drying, pH, specific rotation, crystallinity, and identity.

(ii) Samples of the batch:
(a) If the batch is packaged for repacking or for use as an ingredient in the manufacture of another drug:
(1) For all tests except sterility: 10 packages, each containing at least 500 milligrams.
(2) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.
(b) If the batch is packaged for dispensing:
(1) For all tests except sterility: A minimum of 13 immediate containers of the batch.
(2) For sterility testing: 20 immediate containers collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—
(i) Potency—(i) Sample preparation. Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), for the microbiological agar diffusion assay, distilled water for the iodometric assay or hydroxylamine colorimetric assay, to give a stock solution of convenient concentration; also if it is packaged for dispensing, reconstitute as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with either solution 1 or distilled water as specified above to give a stock solution of convenient concentration.
(ii) Assay procedures. Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.
(a) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with distilled water to the prescribed concentration.

NOTE: The 10 milliliters of 0.01N iodine must be added within 20 seconds after the addition of the 2.0 milliliters of 1.2N HCl, and the assay should be completed within 1 hour after the sample and standard are first put into solution. The working standard should be dried as described in §436.200(a) of this chapter.
(b) Iodometric assay. Proceed as directed in §436.204 of this chapter.
(c) Hydroxylamine colorimetric assay. Proceed as directed in §436.205 of this chapter.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.
(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cephaloridine per milliliter.
(4) Loss on drying. Proceed as directed in §436.200(b) of this chapter.
(5) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 250 milligrams of cephaloridine per milliliter. If it is packaged for dispensing, however, use the solution obtained after reconstituting the drug as directed in the labeling.
(6) Specific rotation. Dilute an accurately weighed sample with sufficient distilled water to give a concentration of approximately 10 milligrams of cephaloridine per milliliter. Proceed as directed in §436.210 of this chapter using a 2.0-decimeter polarimeter tube.
(7) Crystallinity. Proceed as directed in §436.203(a) of this chapter.
(8) Identity. Using a 0.0025-percent solution of the sample in water and a suitable spectrophotometer, record the ultraviolet absorption spectrum from 220 to 310 nanometers. The spectrum compares qualitatively to that of the cephaloridine working standard similarly tested.
§ 442.25a

formed by reaction of thiophene-2-acetic acid with 7-amino-cephalosporanic acid. The 7-amino-cephalosporanic acid is obtained from a kind of cephalosporin. It is so purified and dried that:

(i) Its potency is not less than 850 micrograms of cephalothin per milligram on an anhydrous basis. If it is packaged for dispensing, its potency is satisfactory if it is not less than 50 percent and not more than 115 percent of the number of milligrams of cephalothin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its loss on drying is not more than 1.5 percent.

(vi) Its pH in an aqueous solution is not less than 4.5 and not more than 7.0.

(vii) The specific rotation in an aqueous solution containing 50 milligrams of cephalothin sodium per milliliter at 25°C is $\pm 129°$.

(viii) It gives a positive identity test.

(ix) It is crystalline.

(2) Packaging. In addition to the requirements of § 432.1 of this chapter, if it is packaged for dispensing and is intended for both intravenous and intramuscular use, each vial shall contain the equivalent of 1 gram of cephalothin; except that if it is packaged for dispensing and is intended solely for intravenous use, each vial shall contain the equivalent of 4 grams of cephalothin.

(3) Labeling. In addition to the labeling requirements prescribed by § 432.5 of this chapter, if it is packaged for dispensing, each package shall bear on its label and labeling, the following statement: "After reconstitution, store in a refrigerator and use within 48 hours. If kept at room temperature, use within 6 hours."

(4) Requests for certification; samples. In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of test and assay on the batch for potency, sterility, pyrogens, loss on drying, pH, specific rotation, crystallinity, and identity.

(ii) Samples of the batch:

(a) If the batch is packaged for re-packing or for use as an ingredient in the manufacture of another drug:

(1) For all tests except sterility: 10 packages, each containing equal portions of approximately 500 milligrams.

(2) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 10 immediate containers of the batch.

(2) For sterility testing: 20 immediate containers collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Potency—(i) Sample preparation. Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), for the microbiological agar diffusion assay, distilled water for the iodometric assay or hydroxylamine colorimetric assay, to give a stock solution of convenient concentration; also if it is packaged for dispensing, reconstitute as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with either solution 1 or distilled water as specified above to give a stock solution of convenient concentration.

(ii) Assay procedures. Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(a) Microbiological agar diffusion assay. Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 microgram of cephalothin per milliliter (estimated).

(b) Iodometric assay. Proceed as directed in § 436.204 of this chapter, if it is packaged for dispensing, dilute an aliquot of the stock solution with distilled water to the prescribed concentration.
NOTE: The 10 milliliters of 0.01N iodine must be added within 20 seconds after the addition of the 2.0 milliliters of 1.2N HCl, and the assay should be completed within 1 hour after the sample and standard are first put into solution. The working standard should be dried as described in §436.200(a) of this chapter.

(c) Hydroxylamine colorimetric assay. Proceed as directed in §436.205 of this chapter.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (a)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cephalothin per milliliter.

(4) [Reserved]

(5) Loss on drying. Proceed as directed in §436.200(b) of this chapter.

(6) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 250 milligrams per milliliter; however, if it is packaged for dispensing, use the solution obtained after reconstituting the drug as directed in the labeling.

(7) Specific rotation. Dilute an accurately weighed sample with sufficient distilled water to give a concentration of approximately 50 milligrams per milliliter. Proceed as directed in §436.210 of this chapter, using a 1.0-decimeter polarimeter tube and calculate the specific rotation on an anhydrous basis.

(8) Crystallinity. Proceed as directed in §436.203(a) of this chapter.

(9) Identity. Using a 0.0025-percent solution of the sample in water and a suitable spectrophotometer, record the ultraviolet absorption spectrum from 220 to 310 nanometers. The spectrum compares qualitatively to that of the cephalothin working standard similarly tested.


§ 442.27 Cephalexin monohydrate.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephalexin monohydrate is the monohydrate form of 7-(D-alpha-amino-alpha-phenoxyacetamido)-3-methyl-3-cephem-4-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms of cephalxin per milligram on an anhydrous basis.

(ii) [Reserved]

(iii) Its moisture content is not less than 4.0 nor more than 8.0 percent.

(iv) Its pH in an aqueous solution containing 50 milligrams per milliliter is not less than 3.0 nor more than 5.5.

(v) When calculated on an anhydrous basis, its absorptivity at 262 nanometers is not less than 95 percent and not more than 104 percent of that of the cephalxin standard similarly treated and corrected for potency.

(vi) It gives a positive identity test.

(vii) It is crystalline.

(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution containing 1.0 milligram per milliliter (estimated). Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 20 micrograms of cephalxin per milliliter (estimated).

(ii) Iodometric assay. Proceed as directed in §436.204 of this chapter.

NOTE: The 10 milliliters of 0.01N iodine must be added within 20 seconds after the addition of the 2.0 milliliters of 1.2N hydrochloric acid, and the assay should be completed within 1 hour after the sample and standard are first put into solution.
§ 442.28 Cephalexin hydrochloride monohydrate.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephalexin hydrochloride monohydrate is the hydrochloride salt of 7-[D-alpha-amino-alpha-phenylacetamido]-3-methyl-3-cephem-4-carboxylic acid monohydrate. It is so purified and dried that:

(i) Its potency is not less than 800 micrograms and not more than 880 micrograms of cephalexin per milligram on an "as is" basis.
(ii) Its moisture content is not less than 3.0 nor more than 6.5 percent.
(iii) The pH of an aqueous solution containing 10 milligrams per milliliter is not less than 1.5 nor more than 3.0.
(iv) It gives a positive identity test.
(v) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Moisture. Proceed as directed in § 436.201 of this chapter.

(4) pH. Proceed as directed in § 436.202 of this chapter, using an aqueous suspension containing 50 milligrams per milliliter.

(5) Absorptivity. Determine the absorbance of the sample and standard solutions in the following manner: Dissolve accurately weighed portions of approximately 50 milligrams each of the sample and standard in 250 milliliters of distilled water. Transfer a 10-milliliter aliquot to a 100-milliliter volumetric flask and dilute to volume with distilled water. Using a suitable spectrophotometer and distilled water as the blank, determine the absorbance of each solution at 262 nanometers. Determine the percent absorptivity of the sample relative to the absorptivity of the standard using the following calculations:

\[
\text{Percent relative absorptivity} = \frac{\text{Absorbance of sample} \times \text{Milligrams of sample}}{\text{Absorbance of standard} \times \text{Milligrams of standard}} \times \frac{\text{Potency of standard in micrograms per milligram}}{100 - m}
\]

where \(m\) = percent moisture in the sample.

(6) Identity. Proceed as directed in § 436.211 of this chapter, using the 0.5 percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

(7) Crystallinity. Proceed as directed in § 436.203 of this chapter.


§ 442.29a Sterile cephalpirin sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Sterile cephalpirin sodium is the sodium salt of 7-[alpha(4-pyridylthio)-acetamido]-cephalosporanic acid. It is a white to off-white powder. It is so purified and dried that:

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cephalpirin potency, moisture, pH, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) Tests and methods of assay—(1) Cephalexin potency. Proceed as directed in § 442.40(b)(1)(ii), except that "cephalexin" is substituted at each occurrence of "cephradine".

(2) Moisture. Proceed as directed in § 436.201 of this chapter.

(3) pH. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(4) Identity. Proceed as directed in § 436.367 of this chapter.

(5) Crystallinity. Proceed as directed in § 436.203(a) of this chapter.

[54 FR 48860, Nov. 28, 1989]
(i) Its potency is not less than 855 micrograms and not more than 1,000 micrograms of cephaloridine per milligram on an “as is” basis. If it is packaged for dispensing, its content is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of cephaloridine that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 2.0 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams of cephaloridine per milliliter is not less than 6.5 and not more than 8.5.

(vii) Its cephaloridine content is not less than 92 percent and not more than 105 percent on an anhydrous basis.

(viii) It gives a positive identity test for sodium cephaloridine.

(ix) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, cephaloridine content, identity, and crystallinity.

(ii) Samples required:

(a) If the batch is packaged for repacking or for use in the manufacture of another drug:

(1) For all tests except sterility: 9 packages, each containing approximately 500 milligrams, and 1 package containing approximately 5 grams.

(2) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 14 immediate containers, except if each contains less than 1 gram, a minimum of 19 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(3) Use and methods of assay—(1) Potency. Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration; also, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with solution 1 to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 microgram of cephaloridine per milliliter (estimated).

(ii) Iodometric assay. Proceed as directed in §436.204 of this chapter. In addition if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with distilled water to the prescribed concentration.

(iii) Hydroxylamine colorimetric assay. Proceed as directed in §436.205 of this chapter. In addition, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with distilled water to the prescribed concentration.
§ 442.40  

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 100 milligrams of cephapirin per milliliter.

(4) [Reserved]

(5) Moisture. Proceed as directed in §436.201 of this chapter.

(6) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(7) Cephapirin content. Proceed as directed in §436.213 of this chapter, using the titration procedure described in paragraph (e)(2) of that section. Calculate the cephapirin content as follows:

\[
\text{Percent cephapirin content} = \frac{(A - B) \times (\text{normality of perchloric acid reagent})}{(222.7) \times (100) \times (100 - m)}
\]

where:

\( A \) = Milliliters of perchloric acid reagent used in titrating the sample.

\( B \) = Milliliters of perchloric acid reagent used in titrating the blank.

\( m \) = Percent moisture content of the sample.

(viii) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, cephalexin content, identity, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 500 milligrams.

(b) Tests and methods of assay—(1) Potency. Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution containing 1.0 microgram of cephapirin per milliliter (estimated). Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 10 micrograms of cephapirin per milliliter (estimated).

(ii) Hydroxylamine colorimetric assay for cephapirin—(a) Typical equipment. Use automated equipment capable of
performing the following functions: Introduction of sample into reaction vessels, addition of reagents to the samples to form reaction mixtures, incubation of the reaction mixtures, colorimetric determination of the reaction product at 480 nanometers using a 1-centimeter tubular flow cuvette, and documentation of the results with a strip chart recorder. A suitable system is the Auto Analyzer II equipment consisting of a Solid or Liquid Sampler II, a twenty channel Pump III, a colorimeter equipped with a 1-centimeter tubular flow cuvette and light filters producing incident light at 480 nanometers, and a strip chart recorder with scale expander.

(b) Reagents—(1) Hydroxylamine hydrochloride solution. Dissolve 20 grams of hydroxylamine hydrochloride and 5 milliliters of emulsifying stock solution (prepared to contain 100 milligrams of polyoxyethylene fatty alcohol ether, such as Brij-35 or equivalent, per 100 milliliters distilled water) in sufficient distilled water to make 1 liter.

(2) Buffer. Dissolve 173 grams of sodium hydroxide and 20.6 grams of sodium acetate in sufficient distilled water to make 1 liter. Dilute 75 milliliters of this solution with distilled water to 500 milliliters.

(3) 3.3N Sulfuric acid. Dilute 91 milliliters of concentrated sulfuric acid to 1 liter with distilled water.

(4) Ferric nitrate solution. Dissolve 300 grams of ferric nitrate nonahydrate (9H2O) in a mixture of 2.8 milliliters of concentrated sulfuric acid and sufficient distilled water to make 1 liter.

(c) Preparation of working standard solutions. Dissolve and dilute an accurately weighed portion of the cephradine working standard in sufficient distilled water to obtain a concentration of 1 milligram of cephradine per milliliter.

(d) Preparation of sample solutions. Dissolve an accurately weighed portion of the sample in distilled water and further dilute to 1 milligram of cephradine per milliliter (estimated).

(e) Procedure. Use the standard and sample solutions prepared as indicated in paragraph (b)(1)(ii) (c) and (d) of this section respectively. The arrangement of the apparatus and flow of samples and reagents are shown in the manifold diagram set forth in this paragraph (b)(1)(ii)(e). The sampler rate is usually 40 per hour, but may be varied.
The numbers represent the solutions as follows:

1. Hydroxyamine hydrochloride solution
2. Buffer
3. 3 M Sulfuric acid
4. Ferric nitrate solution

Sample: 0.32
Air: 0.42
Rate: Usually 40 per hour

Milliliters/minute

400 nm.

Coulometer

Recorder
§ 442.40a Sterile cephradine.

(a) Requirements for certification—

(1) Standards of identity, strength, quality, and purity. Cephradine is 7-[D-2-amino-2-(1,4-cyclohexadien-1-yl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 900 and not more than 1,050 micrograms of cephradine per milligram on the anhydrous basis. If it is packaged for dispensing, its cephradine content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cephradine that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 6.0 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 3.5 and not more than 6.0.

(vii) Its cephalexin content is not more than 5 percent on an anhydrous basis.

(viii) It passes the identity test.

(ix) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, cephalexin content, identity, and crystallinity.

(ii) Samples required:

(a) If the batch is packaged for repacking or for manufacturing use:

1. For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

2. For sterility testing: 1 package containing approximately 6 grams of a composite sample.

(b) If the batch is packaged for dispensing:

1. For all tests except sterility: A minimum of 10 immediate containers.

2. For sterilility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—

(1) Potency. Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution containing 1.0 milligram of cephradine per milliliter (estimated); also, if it is packaged for dispensing, reconstitute the sample as directed in the labeling.
§ 442.41 Cephradine dihydrate.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephradine dihydrate is the dihydrate form of \( (6R, 7R)-7-[(R)-2-amino-2-(1,4-cyclohexadien-1-yl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic\) acid. It is so purified and dried that:

   (i) Its potency is not less than 900 micrograms and not more than 1,050 micrograms of cephradine per milligram on an anhydrous basis.
   (ii) Its moisture content is not less than 8.5 percent and not more than 10.5 percent.
   (iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 3.5 and not more than 6.0.
   (v) Its cephalaxin content is not more than 5 percent on an anhydrous basis.
   (vi) It passes the identity test.
   (vii) It is crystalline.

(2) Sterility. Proceed as directed in §436.201 of this chapter.

(3) Pyrogens. Proceed as directed in §436.337 of this chapter.

(b) Tests and methods of assay—(1) Potency. Use any of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

(ii) Hydroxylamine colorimetric assay for cephradine. Proceed as directed in §442.40(b)(1)(ii).

(iii) High-pressure liquid chromatographic assay. Proceed as directed in §436.337 of this chapter, preparing the sample as described in paragraph (e)(3)(i) of that section.

(2) [Reserved]

§ 442.41 Cephradine dihydrate.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephradine dihydrate is the dihydrate form of \( (6R, 7R)-7-[(R)-2-amino-2-(1,4-cyclohexadien-1-yl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic\) acid. It is so purified and dried that:

   (i) Its potency is not less than 900 micrograms and not more than 1,050 micrograms of cephradine per milligram on an anhydrous basis.
   (ii) Its moisture content is not less than 8.5 percent and not more than 10.5 percent.
   (iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 3.5 and not more than 6.0.
   (v) Its cephalaxin content is not more than 5 percent on an anhydrous basis.
   (vi) It passes the identity test.
   (vii) It is crystalline.
§ 442.50a Sterile ceforanide.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Ceforanide is 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[2-(amino-methyl)phenyl]acetyl]amino]-3-[[1-(carboxymethyl)-1H-tetrazol-5-yl]-thio][methyl]-8-oxo-(6R-trans). It is a white to off-white powder. It is so purified and dried that:
   (i) Its ceforanide content is not less than 900 micrograms and not more than 1,050 micrograms of ceforanide per milligram.
   (ii) It is sterile.
   (iii) It is nonpyrogenic.
   (iv) Its moisture content is not more than 5.0 percent.
   (v) Its pH in an aqueous suspension containing 50 milligrams per milliliter is not less than 2.5 and not more than 4.5.
   (vi) It passes the identity test.
(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.
(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:
   (i) Results of tests and assays on the batch for ceforanide content, sterility, pyrogens, moisture, pH, and identity.
   (ii) Samples, if required by the Director, Center for Drug Evaluation and Research:
      (a) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.
      (b) For sterility testing: One package containing approximately 6 grams of a composite sample.
(4) Cephalaxin content. Proceed as directed in §436.337 of this chapter.
(5) Identity. Proceed as directed in §436.211 of this chapter, using the 1 percent potassium bromide disc prepared as described in paragraph (b) of that section.
(6) Crystallinity. Proceed as directed in §436.203(a) of this chapter.

§ 442.52 Cefotetan.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefotetan is \((6R,7S)-4-\{2\text{-carboxy}-7\text{-methoxy}-3\{1\text{-methyl}-1H\text{-tetrazol-5-yl}thio\}\text{methyl}\}_8\text{-oxo-5\text{-thia}-1\text{-azabicyclo}[4.2.0]oct-2\text{-yl}}\text{-carbamoyl}\}_1\text{-3\text{-dithietane}}\text{-}\Delta_2,\alpha\text{-malonamic acid. It is so purified and dried that:}

(i) Its potency is not less than 950 micrograms and not more than 1,030 micrograms of cefotetan activity per milligram on the anhydrous basis.

(ii) Its moisture content is not more than 2.5 percent.

(iii) It gives a positive identity test for cefotetan.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages each containing approximately 500 micrograms.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in §436.216 of this chapter, except use the resolution test solution to determine resolution in lieu of the working standard solution. Perform the assay at ambient temperature, using an ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silicas, a flow rate not exceeding 2.0 milliliters per minute, and a known injection volume of between 10 and 20 microliters. Reagents, working standard solution, sample solution, resolution test solution, system suitability requirements, and calculations are as follows:


(B) Mobile phase. Mix 0.14 phosphoric acid:glacial acetic acid:methanol:acetonitrile (1700:105:105). Filter through a suitable filter capable of removing particulate matter greater than 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) Preparation of working standard, sample, and resolution test solutions—(A) Working standard solution. Accurately weigh approximately 50 micrograms of the cefotetan working standard into a 250-milliliter volumetric flask containing 12.5 milliliters of methanol. Swirl the flask for several minutes, then add 12.5 milliliters of acetonitrile. Swirl the flask until the cefotetan is dissolved. Dilute to volume with water to obtain a solution containing approximately 200 micrograms of cefotetan per milliliter. Mix well. Protect the working standard solution from light.

(B) Sample solution. Dissolve an accurately weighed portion of the sample with sufficient diluting solution described in paragraph (b)(1)(i)(A) of this section to obtain a concentration of approximately 200 micrograms of cefotetan per milliliter.

(C) Resolution test solution. Place 10 milliliters of the working standard solution in a stoppered flask containing a few milligrams of magnesium carbonate. Close the flask and sonicate for 10 minutes. If the solution is not slightly turbid, add more magnesium carbonate and repeat sonication. Filter the turbid solution through a 0.5-micron filter and use within 2 hours. As this solution stands, the tautomer concentration increases.

(iii) System suitability requirements—(A) Tailing factor. The tailing factor \((T)\) is satisfactory if it is not more than 1.3 at 10 percent of peak heigth in lieu of 5 percent of peak height.
(B) Efficiency of the column. The efficiency of the column (n) is satisfactory if it is greater than 1,500 theoretical plates.

(C) Resolution. The resolution (R) between the peak for cefotetan and its tautomer is satisfactory if it is not less than 2.0.

(D) Coefficient of variation. The coefficient of variation (S, in percent) of five replicate injections is satisfactory if it is not more than 2.0 percent. If the system suitability requirements have been met, then proceed as described in §436.216(b) of this chapter. Alternate chromatographic conditions are acceptable provided comparable system suitability requirements are met. However, the sample preparation described in paragraph (b)(1)(ii)(B) of this section should not be changed.

(iv) Calculation. Calculate the micrograms of cefotetan per milligram of sample as follows:

Micrograms of cefotetan per milligram = \( \frac{A_U \times P_S \times V_f \times 1,000}{A_S \times V_s} \)

where:
A_U = Area of the cefotetan peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
A_S = Area of the cefotetan peak in the chromatogram of the cefotetan working standard;
P_S = Cefotetan activity in the cefotetan working standard solution in micrograms per milliliter;
V_f = Volume of flask used to dilute standard; and
V_s = Volume of sample diluted.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) Identity. Proceed as directed in §436.211 of this chapter using the potassium bromide discs prepared as described in §436.211(b)(1) of this chapter or the mineral oil mull prepared as described in §436.211(b)(2) of this chapter.

[59 FR 26940, May 25, 1994, as amended at 60 FR 33712, June 29, 1995]

§ 442.53a Sterile cefotetan disodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Sterile cefotetan disodium is a white to off-white lyophilized powder. It is so purified and dried that:

(i) If the cefotetan disodium is not packaged for dispensing, its potency is not less than 830 micrograms and not more than 970 micrograms of cefotetan per milligram on the anhydrous basis. If the cefotetan disodium is packaged for dispensing, its potency is not less than 830 micrograms and not more than 970 micrograms of cefotetan per milligram on the anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefotetan that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 1.5 percent.

(v) Its pH in an aqueous solution containing 100 milligrams of cefotetan disodium per milliliter is not less than 4.0 and not more than 6.5.

(vi) It gives a positive identity test for cefotetan.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) If the batch is packaged for repacking or for use in the manufacture of another drug:

(1) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(2) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in §436.216 of this chapter, except use the resolution test solution to determine resolution.
in lieu of the working standard solution. Perform the assay at ambient temperature, using an ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silicas, a flow rate not exceeding 2.0 milliliters per minute, and a known injection volume of between 10 and 20 microliters. Reagents, working standard solution, sample solution, resolution test solution, system suitability requirements, and calculations are as follows:


(b) Mobile phase. Mix 0.1N phosphoric acid:glacial acetic acid:methanol:acetonitrile (1700:100:105:105). Filter through a suitable filter capable of removing particulate matter greater than 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) Preparation of working standard, sample, and resolution test solutions—(a) Working standard solution. Accurately weigh approximately 50 milligrams of the cefotetan working standard into a 250-milliliter volumetric flask containing 12.5 milliliters of methanol. Swirl the flask for several minutes, then add 12.5 milliliters of acetonitrile. Swirl the flask until the cefotetan is dissolved. Dilute to volume with water to obtain a solution containing approximately 200 micrograms of cefotetan per milliliter. Mix well. Protect the working standard solution from light.

(b) Sample solutions—(1) Product not packaged for dispensing (micrograms of cefotetan per milligram). Dissolve an accurately weighed portion of the sample with sufficient diluting solution described in paragraph (b)(1)(i) of this section, to obtain a concentration of approximately 200 micrograms of cefotetan per milliliter.

(2) Product packaged for dispensing. Determine both micrograms of cefotetan per milligram of the sample and milligrams of cefotetan per container. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(i)(b)(1) and (ii) of this section.

(i) Micrograms of cefotetan per milligram. Dissolve an accurately weighed portion of the sample with sufficient diluting solution described in paragraph (b)(1)(i)(a) of this section, to obtain a concentration of approximately 200 micrograms of cefotetan per milliliter.

(ii) Milligrams of cefotetan per container. Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Further dilute an aliquot of the solution thus obtained with sufficient diluting solution described in paragraph (b)(1)(i)(a) of this section, to obtain a concentration of approximately 200 micrograms of cefotetan per milliliter.

(c) Resolution test solution. Place 10 milliliters of the working standard solution in a stoppered flask containing a few milligrams of magnesium carbonate. Close the flask and sonicate for 10 minutes. If the solution is not slightly turbid, add more magnesium carbonate and repeat sonication. Filter the turbid solution through a 0.5-micron filter and use within 2 hours. As this solution stands, the tautomer concentration increases.

(iii) System suitability requirements—(a) Tailing factor. The tailing factor (T) is satisfactory if it is not more than 1.3 at 10 percent of peak height in lieu of 5 percent of peak height.

(b) Efficiency of the column. The efficiency of the column (N) is satisfactory if it is greater than 1,500 theoretical plates.

(c) Resolution. The resolution (R) between the peak for cefotetan and its tautomer is satisfactory if it is not less than 2.0.

(d) Coefficient of variation. The coefficient of variation (S in percent) of five replicate injections is satisfactory if it is not more than 2.0 percent.

If the system suitability requirements have been met, then proceed as described in §436.216(b) of this chapter. Alternate chromatographic conditions
are acceptable provided comparable system suitability requirements are met. However, the sample preparation described in paragraph (b)(1)(ii)(b) of this section should not be changed.

(iv) Calculations—(a) Calculate the micrograms of cefotetan per milligram of sample as follows:

\[
\text{Micrograms of cefotetan per milligram} = \frac{A_u \times P_s \times 100}{A_s \times (100 - m)}
\]

where:

- \(A_u\) = Area of the cefotetan peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the cefotetan peak in the chromatogram of the cefotetan working standard;
- \(P_s\) = Cefotetan activity in the cefotetan working standard solution in micrograms per milliliter;
- \(C_u\) = Milligrams of sample per milliliter of sample solution; and
- \(m\) = Percent moisture content of the sample.

(b) Calculate the cefotetan content of the container as follows:

\[
\text{Milligrams of cefotetan per container} = \frac{A_u \times P_s \times d}{A_s \times 1,000}
\]

where:

- \(A_u\) = Area of the cefotetan peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the cefotetan peak in the chromatogram of the cefotetan working standard;
- \(P_s\) = Cefotetan activity in the cefotetan working standard solution in micrograms per milliliter; and
- \(d\) = Dilution factor of the sample.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cefotetan per milliliter.

(4) Moisture. Proceed as directed in §436.201 of this chapter.

(5) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams of cefotetan disodium per milliliter.

(6) Identity. The high-performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section, compares qualitatively to that of the cefotetan working standard.


§ 442.54 Cefpodoxime proxetil.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefpodoxime proxetil is (±)-1-hydroxyethyl-(+)-(6R,7R)-7-[(2-(4-amino-4-thiazolyl)glyoxylamido)3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate]-2-(Z)-(O-methyloxime), isopropyl carbonate (ester). It is so purified and dried that:

(i) Its potency is not less than 690 micrograms and not more than 804 micrograms of cefpodoxime activity per milligram, on an anhydrous basis.

(ii) The ratio of its R-epimer to total cefpodoxime is not less than 0.5 and not more than 0.6.

(iii) Its moisture content is not more than 3 percent.

(iv) It gives a positive identity test.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in §436.216 of this chapter, using a suitable thermostatted column heating mechanism to maintain a column temperature of 40 °C, an ultraviolet detection system operating at a wavelength of 254 nanometers, a 15 centimeter X 4.6 millimeter (i.d.) column packed with microparticulate (5 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded to silicas, a flow rate of 0.8 milliliter per minute, and a known injection volume of 2 microliters. The retention time for the S-epimer is approximately 22 minutes and the retention time for R-epimer is approximately 28 minutes.
§ 442.54 21 CFR Ch. I (4-1-96 Edition)

The internal standard (propylparaben) has a retention time of 34 minutes. Mobile phase, dilution solvent, resolution solution, internal standard solution, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) Mobile phase. The mobile phase consists of 420 milliliters of methanol, 580 milliliters of deionized water, and 230 milligrams of L-histidine hydrochloride. The pH is adjusted to 2.5 ± 0.1 using 2N sulfuric acid. The mobile phase must be at room temperature for a correct pH measurement. The methanol concentration may be adjusted to achieve comparable retention times from column to column. Increasing methanol reduces retention times. Filter the mobile phase through a suitable filter capable of removing particulate matter 0.5 micron in diameter and degas it just before its introduction into the chromatograph.

(ii) Dilution solvent. Prepare a solvent for dilution by thoroughly mixing 495 milliliters of deionized water, 495 milliliters of acetonitrile, and 10 milliliters of acetic acid in an appropriate container.

(iii) Resolution solution. Prepare a 1 milligram per milliliter solution of any bulk containing ANTI-A in dilution solvent. Use this solution to determine the resolution between ANTI-A and the later-eluting drug epimer (R-epimer). Alternately, the resolution factor can be determined between the R and S iso-omers.

(iv) Internal standard solution. Prepare a solution of propylparaben in dilution solvent at a concentration of 10 milligrams per milliliter.

(v) Preparation of working standard solutions. Accurately weigh approximately 42 milligrams of the cefpodoxime proxetil working reference standard add 3 milliliters of internal standard solution and 25 milliliters of dilution solvent. The standard solution is stable for at least 48 hours. Refrigeration is not recommended.

(vi) Sample solution. Accurately weigh approximately 42 milligrams of the sample, add 3 milliliters of internal standard and 25 milliliters of dilution solvent. The sample solution is stable for at least 48 hours. Refrigeration is not recommended.

(vii) System suitability requirements—

(A) Asymmetry factor. The asymmetry factor (A_s) is satisfactory if it is not less than 0.8 and not more than 1.1 for the R-epimer of cefpodoxime peak.

(B) Efficiency of the column. The absolute efficiency (h_r) is satisfactory if it is not more than 5 for the R-epimer peak.

(C) Resolution factor. The resolution factor (R) between the peak for ANTI-A and the peak for the R-epimer is satisfactory if it is not less than 1.3. Alternately, the resolution factor (R) between the peak for the R-epimer and the peak for the S-epimer of cefpodoxime is not less than 11.

(D) Coefficient of variation (Relative standard deviation). The coefficient of variation (S_R in percent of 5 replicate injections) is satisfactory if it is not more than 2 percent.

(E) Capacity factor (k'). The capacity factor (k') for the R-epimer of cefpodoxime is satisfactory if it is not less than 10.4 and not more than 15.6.

(F) If the system suitability parameters in this paragraph (b)(1)(iv) have been met, then proceed as described in §436.216(b) of this chapter.

(viii) Calculations. Calculate the micrograms of cefpodoxime proxetil per milligram of sample on an anhydrous basis as follows:

\[
\text{Micrograms of cefpodoxime proxetil per milligram} = \frac{R_u \times P_u \times 100}{R_s \times C_s \times (100 - m)}
\]

where:

- \( R_u \) = Ratio of cefpodoxime proxetil peaks area (sum of both epimers) to the internal standard peak response in the sample solution;
- \( R_s \) = Ratio of cefpodoxime proxetil peaks area (sum of both epimers) to the internal standard peak response in the working standard solution;
Food and Drug Administration, HHS

§ 442.55 Ceftriaxone sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Ceftriaxone sodium is the 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[2-amino-4-thiazolyl](methoxyimino)acetyl]amino]-8-oxo-3-[[1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl]thio]methyl]-,disodium salt, [6α,7ß(Z)]. It is so purified and dried that:

(i) Its ceftriaxone potency is not less than 795 micrograms of ceftriaxone per milligram on an anhydrous free acid basis.

(ii) Its moisture content is not less than 8 percent and not more than 11 percent.

(iii) The pH of an aqueous solution containing the equivalent of 100.0 milligrams per milliliter is not less than 6.0 and not more than 8.0.

(iv) It is crystalline.

(v) It gives a positive identity test for ceftriaxone.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for ceftriaxone potency, moisture, pH, crystallinity, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) Tests and methods of assay—(1) Ceftriaxone potency. Proceed as directed in §442.55a(b)(1) of this chapter, except prepare the sample solution and calculate the micrograms of ceftriaxone free acid per milligram as follows:

(i) Preparation of sample solution. Dissolve an accurately weighed portion of the sample in 30 milliliters of solvent C instead of 20 milliliters of solvent A.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(4) Crystallinity. Proceed as directed in §436.203(a) of this chapter.
§ 442.55a Sterile ceftriaxone sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Ceftriaxone sodium is 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[2-amino-4-thiazolyl](methoxyimino)acetyl]amino]-8-oxo-1,2,4-triazin-3-ylthio)methyl]-, disodium salt, [6α,7β(Z)]. It is so purified and dried that:

(a) If the ceftriaxone sodium is not packaged for dispensing, its ceftriaxone potency is not less than 795 micrograms of ceftriaxone per milligram on an anhydrous free acid basis. If the ceftriaxone sodium is packaged for dispensing, its ceftriaxone potency is not less than 776 micrograms of ceftriaxone per milligram on an anhydrous free acid basis and also, each container contains not less than 90 percent and not more than 115 percent of the number of milligrams of ceftriaxone that it is represented to contain.

(b) It is sterile.

(c) It is nonpyrogenic.

(d) Its moisture content is not less than 8 percent and not more than 11 percent.

(e) Its pH in an aqueous solution containing the equivalent of 100.0 milligrams per milliliter is not less than 6.0 and not more than 8.0.

(f) It is crystalline.

(g) It gives a positive identity test for ceftriaxone.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(b) Tests and methods of assay—(1) Ceftriaxone potency and container content. Proceed as directed in §436.354 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 270, 254 nanometers (fixed mercury source), and a column packed with a five-micron octadecyl reverse phase packing or equivalent; and also, using the following system suitability requirements, reagents, working standard, test and sample solutions, and calculations:

(i) System suitability requirements—(a) Capacity factor. The capacity factor (k) for the ceftriaxone peak is satisfactory if it is not less than 2 and not more than 5.

(b) Resolution. The resolution (R) between the peak for ceftriaxone E-isomer and ceftriaxone is satisfactory if it is not less than 3.0.

(c) Asymmetry factor. The asymmetry factor (Aₚ) is satisfactory if it is not more than 1.6 at 10 percent of the peak height.

(d) Efficiency of the column. The efficiency of the column (hₜ) is satisfactory if it is less than 20 (equivalent to a value of 1,500 or greater theoretical plates when using a 15-centimeter column with 5-micrometer-size particles).

(e) Coefficient of variation. The coefficient of variation (Sₐ in percent) of five replicate injections is satisfactory if it is less than 2.0 percent.
If the system suitability parameters have been met, then proceed as described in §436.354(b) of this chapter.

(ii) Reagents—(a) pH 7.0 phosphate buffer. Dissolve 13.6 grams of dibasic potassium phosphate and 4.0 grams of monobasic potassium phosphate in sufficient water to make 1,000 milliliters. Adjust to pH 7.0 ±0.1 with 1N phosphoric acid or 10N potassium hydroxide.

(b) pH 5.0 citrate buffer. Dissolve 25.8 grams of sodium citrate in 500 milliliters of water. Adjust the pH to 5.0 ±0.1 with 20 percent aqueous citric acid, and dilute to 1,000 milliliters with water.

(c) Mobile phase. Dissolve 4.0 grams of tetraheptylammonium bromide with 500 milliliters of acetonitrile. Add 440 milliliters of pH 7.0 phosphate buffer, and 5 milliliters of pH 5.0 citrate buffer. Mix and dilute 800 milliliters of this solution with 200 milliliters of distilled water. Filter the mobile phase through a suitable glass fiber filter or equivalent which is capable of removing particulate contamination greater than 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(iii) Working standard and sample solutions—(a) Preparation of working standard solution. Dissolve an accurately weighed portion of the ceftriaxone working standard with sufficient water to obtain a solution containing approximately 180 micrograms of ceftriaxone activity per milliliter. Prepare the working standard solution just prior to its introduction into the chromatograph.

(b) Preparation of test solution. Dissolve together accurately weighed portions of the ceftriaxone working standard and the ceftriaxone sodium E-isomer reference standard with sufficient water to obtain a solution containing approximately 180 micrograms of ceftriaxone activity per milliliter of each standard. Prepare the test solution just prior to its introduction into the chromatograph.

(c) Preparation of sample solution. Prepare the sample solution just prior to its introduction into the chromatograph.

(i) Product not packaged for dispensing (micrograms of ceftriaxone anhydrous free acid per milligram). Dissolve an accurately weighed portion of the sample with sufficient water to obtain a concentration of 180 micrograms of ceftriaxone activity per milliliter.

(ii) Product packaged for dispensing. Determine both potency (micrograms of ceftriaxone anhydrous free acid per milligram of the sample) and container content (milligrams of anhydrous free acid ceftriaxone per container). Use separate containers for preparation of each sample solution as described in paragraph (b)(1)(iii)(b)(2) (i) and (ii) of this section.

(i) Micrograms of ceftriaxone anhydrous free acid per milligram. Dissolve an accurately weighed portion of the sample with sufficient water to obtain a concentration of approximately 180 micrograms of ceftriaxone activity per milliliter.

(ii) Milligrams of ceftriaxone per container. Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the potency contained in a given volume of the resulting preparation, remove an accurately measured representative portion from each container. Dilute the aliquot of the solution thus obtained with sufficient water to obtain a concentration of approximately 180 micrograms of ceftriaxone activity per milliliter.

(iv) Calculations. (a) Calculate the micrograms of ceftriaxone anhydrous free acid per milligram as follows:

\[
\text{Micrograms of ceftriaxone anhydrous} = \frac{A_u \times P_u}{A_s \times C_u}
\]

where:

- \(A_u\) = Area of the ceftriaxone peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the ceftriaxone peak in the chromatogram of the ceftriaxone working standard;
- \(P_u\) = Ceftriaxone activity in the ceftriaxone working standard solution in micrograms of anhydrous free acid per milliliter; and
- \(C_u\) = Milligrams of sample per milliliter of sample solution.
§ 442.58a Sterile cefotiam dihydrochloride.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefotiam dihydrochloride is 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[2-amino-4-thiazolyl]acetyl]-amino-3-[[1-[2-(dimethylamino)ethyl]-1H-tetrazol-5-y1]thio[methyl]-8-oxo-, dihydrochloride, (6R-trans). It is so purified and dried that:

(i) Its potency is not less than 790 and not more than 925 micrograms of cefotiam per milligram on an anhydrous basis.
(ii) It is sterile.
(iii) It is nonpyrogenic.
(iv) Its moisture content is not more than 7.0 percent.
(v) It passes the identity test.
(vi) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(B) For sterility testing: One package containing approximately 6 grams of a composite sample.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in §436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silicas, a flow rate not to exceed 2.0 milliliters per minute, and a known injection volume of between 10 and 20 microliters. Mobile phase, working standard and sample solutions, resolution test solution, system suitability requirements, and calculations are as follows:

(i) Mobile phase. Dissolve 13.1 grams of ammonium sulfate in 850 milliliters of water. Adjust the pH to 6.5 with dilute aqueous ammonia. Add 130 milliliters of acetonitrile. Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) Preparation of working standard, sample, and resolution test solutions—(A)
Working standard solution. Dissolve approximately 100 milligrams of the cefotiam working standard, accurately weighed, in water and dilute to 100 milliliters. Further dilute with mobile phase to obtain a solution containing 50 micrograms of cefotiam activity per milliliter.

(B) Sample solution. Dissolve approximately 100 milligrams of the sample, accurately weighed, in water and dilute to 100 milliliters. Further dilute with mobile phase to obtain a solution containing 50 micrograms of cefotiam activity per milliliter (estimated).

(C) Resolution test solution. Dissolve an accurately weighed portion of cefotiam working standard in water to obtain a solution containing approximately 1.0 milligram of cefotiam activity per milliliter. Heat this solution at 95°C for 15 minutes. This procedure allows cefotiam lactone to be produced. Dilute 1.0 milliliter of this solution to 100 milliliters with mobile phase.

(iii) System suitability requirements—
(A) Tailing factor. The tailing factor (T) for the cefotiam peak is satisfactory if it is not more than 1.76 at 5 percent of peak height.

(B) Efficiency of the column. The efficiency of the column (n) is satisfactory if it is greater than 1985 theoretical plates for the cefotiam peak.

(C) Resolution factor. The resolution factor (R) between the peak for cefotiam and the peak for cefotiam lactone (generated in situ) is satisfactory if it is not less than 4.0.

(D) Coefficient of variation. The coefficient of variation (S, in percent) of 5 replicate injections is satisfactory if it is not more than 1.0 percent. If the system suitability parameters have been met, then proceed as described in §436.216(b) of this chapter.

(iv) Calculations. Calculate the micrograms of cefotiam per milligram of sample as follows:

$$\text{Micrograms of cefotiam per milligram} = \frac{A_w \times P_s \times 100}{A_c \times C_s \times (100 - m)}$$

where:
- \(A_w\) = Area of the cefotiam peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_c\) = Area of the cefotiam peak in the chromatogram of the cefotiam working standard;
- \(P_s\) = Cefotiam activity in the cefotiam working standard solution in micrograms per milliliter;
- \(C_s\) = Milligrams of the sample per milliliter of sample solution; and
- \(m\) = Percent moisture content of the sample.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(g) of this chapter, using a solution containing 40 milligrams per milliliter.

(4) Moisture. Proceed as directed in §436.201 of this chapter, using the sample preparation described in paragraph (d)(4) of that section and the titration procedure described in paragraph (e)(3) of that section, except:

(i) In lieu of 3 milliliters of anhydrous methanol solution, inject 20 milliliters of a formamide:methanol solution (2:1) into the container and shake to dissolve the contents (prior to use in preparation of the formamide:methanol solution, dry 500 grams of formamide over 20 grams of anhydrous sodium sulfate for 24 hours);

(ii) Rinse the syringe, needle, and immediate container with two separate 5-milliliter portions of anhydrous methanol, in lieu of one 3-milliliter portion of anhydrous methanol; and

(iii) In paragraph (e)(3) of that section, add a sufficient volume of the formamide:methanol solution (2:1) to cover the electrodes in the dry titrating vessel, in lieu of 20 milliliters of solvent A before starting the titration.
§ 442.60 Cefpiramide.

(a) Requirements for certification—

(1) Standards of identity, strength, quality, and purity. Cefpiramide is \((6R, 7R)-7\)-(\((R)-2-(4-hydroxy-6-methylnicotinamido)\)-2-(\((p-hydroxyphenyl)acetamido)\)-3\(\{(1-methyl-1H-tetrazol-5-yl)methyl\}B-oxo-5-thia-1-azabicyclo\[4.2.0\]oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 974 micrograms of cefpiramide activity per milligram on an anhydrous basis.

(ii) Its moisture content is not more than 9.0 percent.

(iii) Its pH in an aqueous suspension containing 5 milligrams per milliliter is not less than 3.0 and not more than 5.0.

(iv) Its total related substances content by high performance liquid chromatography is not more than 2.0 percent. No individual impurity is more than 0.7 percent.

(v) The specific rotation in dimethylformamide solution containing 10 milligrams of cefpiramide per milliliter is \(-106 ± 6^\circ C\) calculated on an anhydrous basis.

(vi) It passes the identity test.

(vii) It is crystalline.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, total related substances, specific rotation, identity, and crystallinity.

(ii) Samples, if required by the Center for Drug Evaluation and Research:

10 packages each containing approximately 500 milligrams.

(b) Tests and methods of assay—

(1) Potency. Proceed as directed in §436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating to a wavelength of 254 nanometers, a 15- to 30-centimeter \(X\) 4-millimeter (inside diameter) column packed with microparticulate (5 to 10 micrometers in diameter) reversed phase packing material such as octylsilane bonded to silica, a flow rate not to exceed 2.0 milliliters per minute, and a known injection volume of between 10 and 20 microliters.

Reagents, working standard and sample solutions, resolution test solution, system suitability requirements, and calculations are as follows:

(i) Reagents—

(A) 0.01M phosphate buffer. Dissolve 1.36 grams of monobasic potassium phosphate in 900 milliliters of water. Adjust the pH to 6.8 with 1N sodium hydroxide and dilute to 1,000 milliliters with water.

(B) Mobile phase. Mix 0.01M phosphate buffer: acetonitrile: tetrahydrofuran: methanol (880:40:40:40). Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) Preparation of working standard, sample, and resolution test solutions—

(A) Working standard solution. Dissolve and dilute an accurately weighed portion of the cefpiramide working standard in anhydrous sodium hydroxide and dilute to 1,000 milliliters with water.

(B) Mobile phase. Mix 0.01M phosphate buffer: acetonitrile: tetrahydrofuran: methanol (880:40:40:40). Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(C) Resolution test solution. Dissolve an accurately weighed portion of the sample in mobile phase and further dilute to 0.25 milligram of cefpiramide per milliliter (estimated).

1.0 milliliter of this solution to 20 milliliters with mobile phase.
(iii) System suitability requirements—
(A) Asymmetry factor. Calculate the asymmetry factor \( A_s \), measured at a point 5 percent of the peak height from the baseline as follows:

\[
A_s = \frac{a + b}{2a}
\]

where:
- \( a \) = Horizontal distance from point of ascent to point of maximum peak height;
- \( b \) = Horizontal distance from the point of maximum peak height to point of descent.

The asymmetry factor \( A_s \) is satisfactory if it is not less than 0.95 and not more than 1.4.

(B) Efficiency of the column. From the number of theoretical plates \( n \) calculated as described in §436.216(c)(2) of this chapter calculate the reduced plate height \( h_r \) as follows:

\[
h_r = \frac{(10,000)(L)}{(n)(d_p)}
\]

where:
- \( L \) = Length of the column in centimeters;
- \( n \) = Number of theoretical plates; and
- \( d_p \) = Average diameter of the particles in the analytical column packing in micrometers.

The absolute efficiency \( h_r \) is satisfactory if it is not more than 12.5 for the cefpiramide peak.

(C) Resolution factor. The resolution factor \( R \) between the peak for cefpiramide and the peak for cefpiramide lactone (generated in situ) is satisfactory if it is not less than 6.0.

(D) Coefficient of variation (relative standard deviation). The coefficient of variation \( S_r \) is satisfactory if it is not more than 2.0 percent.

(E) Capacity factor \( k' \). Calculate the capacity \( k' \) for cefpiramide as follows:

\[
k' = \frac{t_r - t_o}{t_o}
\]

where:
- \( t_r \) = Retention time of cefpiramide in minutes; and
- \( t_o \) = Column dead time in minutes, which is estimated from the following equation:

\[
t_o = \frac{(3.1416)(D^2)(L)(0.75)}{4F}
\]

where:
- \( D \) = Column diameter in centimeters;
- \( L \) = Column length in centimeters;
- 0.75 = Average total column porosity; and
- \( F \) = Flow rate in milliliters per minute.

The capacity factor \( k' \) for cefpiramide is satisfactory if it is not less than 2.0 and not more than 3.0. If the system suitability parameters have been met, then proceed as described in §436.216(b) of this chapter.

(iv) Calculations. Calculate the micrograms of cefpiramide per milligram of sample as follows:

\[
\text{Micrograms of cefpiramide} = \frac{A_u \times P \times 100}{A_s \times C_u \times (100 - m)}
\]

where:
- \( A_u \) = Area of the cefpiramide peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \( A_s \) = Area of the cefpiramide peak in the chromatogram of the cefpiramide working standard;
- \( P \) = Cefpiramide activity in the cefpiramide working standard solution in micrograms per milliliter;
- \( C_u \) = Milligrams of cefpiramide sample per milliliter of sample solution; and
- \( m \) = Percent moisture content of the sample.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using an aqueous suspension containing 5 milligrams of cefpiramide per milliliter.

(4) Total related substances. Proceed as directed in paragraph (b)(1) of this section except use the following reagents, standard and sample solutions, and calculations:

(i) Reagents—(A) 0.03M phosphate buffer. Dissolve 4.08 grams of monobasic potassium phosphate in 800 milliliters of water. Adjust the pH to 7.5 with 1N sodium hydroxide and dilute to 1,000 milliliters with water.

(B) Mobile phase. Mix 0.03M phosphate buffer: methanol (750:250). Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) Preparation of working standard and sample solutions.
§ 442.69  Cefmetazole.

(a) Requirements for certification—
(1) Standards of identity, strength, quality, and purity. Cefmetazole is \((6R,7S)-7\{(cyanomethyl)thio\}acetamido\}-7-methoxy-3\{[(1-methyl-1H-tetrazol-5-yl)thio]methyl\}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that:
   (i) Its potency is not less than 970 micrograms of cefmetazole activity per milligram.
   (ii) Its moisture content is not more than 0.5 percent.
   (iii) It gives a positive identity test for cefmetazole.
(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.
(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:
   (i) Results of tests and assays on the batch for potency, moisture, and identity.
   (ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages each containing approximately 500 milligrams.
(b) Tests and methods of assay—
(1) Potency. Proceed as directed in §442.70a(b)(1).

[55 FR 14240, Apr. 17, 1990]
§ 442.70a Sterile cefmetazole sodium.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Sterile cefmetazole sodium is the sodium salt of \((6R\text{-cis})-7-((\text{cyanomethyl})\text{thio})\text{acetyl})\text{amino}\)-7-methoxy-3\-\(1\text{-methyl-1H-tetrazol-5-yl})\text{thio)methyl})\text{8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is a lyophilized powder. It is so purified and dried that:

(i) If the cefmetazole sodium is not packaged for dispensing, its cefmetazole potency is not less than 860 micrograms and not more than 1,003 micrograms of cefmetazole activity per milligram on an anhydrous basis. If the cefmetazole sodium is packaged for dispensing, its cefmetazole potency is not less than 860 micrograms and not more than 1,003 micrograms of cefmetazole activity per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefmetazole that it is represented to contain.

(ii) It is sterile.

(iii) It contains not more than 0.2 endotoxin units per milligram.

(iv) Its moisture content is not more than 0.5 percent.

(v) The pH of an aqueous solution containing 100 milligrams per milliliter is not less than 4.2 and not more than 6.2.

(vi) It gives a positive identity test.

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefmetazole potency and content (if packaged for dispensing), sterility, bacterial endotoxins, moisture, pH, and identity.

(ii) Samples, if required by the Center for Drug Evaluation and Research: (A) If the batch is packaged for re-packing or for use as an ingredient in the manufacture of another drug:

(1) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(2) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.

(B) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 10 immediate containers of the batch.

(2) For sterility testing: 20 immediate containers collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 214 nanometers, a 25-centimeter X 4.0- or 4.6-millimeter (inside diameter) column packed with microparticulate (5 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded to silicas, a flow rate of not more than 2.0 milliliters per minute, and a known injection volume of between 10 and 20 microliters. Mobile phase, working standard and sample solutions, resolution test solution, system suitability requirements, and calculations are as follows:

(i) Mobile phase. Transfer 5.75 grams of ammonium dihydrogen phosphate to a 1-liter container. Add 700 milliliters of deionized water and agitate to aid dissolution. Transfer 3.2 milliliters of tetrabutylammonium hydroxide (TBAH) in distilled water to the solution and shake. Add 280 milliliters of methanol and a range 20 to 30 milliliters of tetrahydrofuran and mix well. Adjust the pH to 4.5±0.1 with phosphoric acid. The mobile phase is 0.05M ammonium dihydrogen phosphate: methanol: tetrahydrofuran (700:280:20-30). It is 0.005M with respect to TBAH. Filter the mobile phase through a suitable filter capable of removing particulate matter to 0.5 micron in diameter and degas it just prior to its introduction into the chromatograph.

(ii) Preparation of working standard, sample, and resolution test solutions—(A) Working standard solution. Dissolve and
dilute and accurately weighed portion of the cefmetazole working standard in sufficient mobile phase to obtain a solution containing 0.2 milligram of cefmetazole activity per milliliter. Analyze this solution within 10 minutes.

(B) Sample solutions—(1) Product not packaged for dispensing (micrograms of cefmetazole per milligram). Dissolve an accurately weighed sample with sufficient mobile phase to obtain a solution containing approximately 0.2 milligram of cefmetazole per milliliter (estimated). Analyze this solution within 10 minutes.

(2) Product packaged for dispensing. Determine both micrograms of cefmetazole per milligram of sample and milligrams of cefmetazole per container. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(ii)(B)(2)(i) and (ii) of this section.

(i) Micrograms of cefmetazole per milligram. Dissolve an accurately weighed sample with sufficient mobile phase to obtain a solution containing approximately 0.2 milligram of cefmetazole per milliliter (estimated). Analyze this solution within 10 minutes.

(ii) Milligrams of cefmetazole per container. Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute the solution thus obtained with sufficient distilled water to obtain a solution containing 1,000 micrograms of cefmetazole activity per milliliter (estimated). Further dilute this solution with mobile phase to obtain a solution containing 0.2 milligram of cefmetazole activity per milliliter (estimated). Analyze this solution within 10 minutes.

(C) Resolution test solution. Dissolve an accurately weighed portion of cefmetazole working standard in 0.01N sodium hydroxide to obtain a solution containing approximately 1.0 milligram of cefmetazole activity per milliliter. Heat this solution at 95 °C for 10 minutes. This procedure generates cefmetazole lactone. Dilute 1.0 milliliter of this solution to 20 milliliters with mobile phase.

(iii) System suitability requirements—

(A) Asymmetry factor. Calculate the asymmetry factor \(A_s\), measured at a point 10 percent of the peak height from the baseline as follows:

\[ A_s = \frac{a+b}{2a} \]

where:

\(a\) = Horizontal distance from point of ascent to point of maximum peak height; and
\(b\) = Horizontal distance from point of maximum peak height to point of descent.

The asymmetry factor \(A_s\) is satisfactory if it is not less than 0.94 and not more than 1.6.

(B) Efficiency of the column. From the number of theoretical plates \(n\) calculated as described in §436.216(c)(2) of this chapter calculate the reduced plate height \(h_r\) as follows:

\[ h_r = \frac{(L)(10,000)}{(n)(d_p)} \]

where:

\(L\) = Length of the column in centimeters;
\(n\) = Number of theoretical plates; and
\(d_p\) = Average diameter of the particles in the analytical column packing in micrometers.

The absolute efficiency \(h_r\) is satisfactory if it is not more than 20 for the cefmetazole peak.

(C) Resolution factor. The resolution factor \(R\) between the peak for cefmetazole and the peak for cefmetazole lactone (generated in situ) is satisfactory if it is not less than 3.0.

(D) Coefficient of variation (relative standard deviation). The coefficient of variation \(S_{xR}\) in percent of 5 replicate injections) is satisfactory if it is not more than 2.0 percent.

(E) Capacity factor \(k'\). Calculate the capacity factor \(k'\) for cefmetazole as follows:
\[ k' = \frac{t_r - t_o}{t_o} \]

where:
- \(t_r\) = Retention time of cefmetazole in minutes;
- \(t_o\) = Column dead time in minutes, which is estimated from the following equation:

\[ t_o = \frac{(3.1416)(D^2)(L)(0.75)}{4F} \]

where:
- \(D\) = Column diameter in centimeters;
- \(L\) = Column length in centimeters;
- 0.75 = Average total column porosity; and
- \(F\) = Flow rate in milliliters per minute.

The capacity factor \((k')\) for cefmetazole is satisfactory if it is not less than 2.0 and not more than 8.0. If the system suitability parameters have been met, then proceed as described in §436.216(b) of this chapter.

(iv) Calculations—(A) Cefmetazole potency (micrograms of cefmetazole per milligram). Calculate the micrograms of cefmetazole per milligram of sample as follows:

\[
\text{Micrograms of cefmetazole per milligram} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - m)}
\]

where:
- \(A_u\) = Area of the cefmetazole peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the cefmetazole peak in the chromatogram of the cefmetazole working standard;
- \(P_s\) = Cefmetazole activity in the cefmetazole working standard solution in micrograms per milliliter; and
- \(m\) = Percent moisture content of the sample.

(B) Cefmetazole content (milligrams of cefmetazole per container). Calculate the cefmetazole content of the container as follows:

\[
\text{Milligrams of cefmetazole per container} = \frac{A_u \times P_s}{A_s \times 1,000}
\]

where:
- \(A_u\) = Area of the cefmetazole peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the cefmetazole peak in the chromatogram of the cefmetazole working standard;
- \(P_s\) = Cefmetazole activity in the cefmetazole working standard solution in micrograms per milliliter; and
- \(d\) = Dilution factor of the sample.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in §436.20(e)(1).

(3) Bacterial endotoxins. Proceed as directed in the United States Pharmacopeia bacterial endotoxins test.

(4) Moisture. Proceed as directed in §436.201 of this chapter.

(5) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(6) Identity. Proceed as directed in §436.211 of this chapter using a mineral oil mull prepared as described in §436.211(b)(2).

[55 FR 6634, Feb. 26, 1990]

§ 442.80 Cefprozil.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefprozil is an approximate 9:1 mixture of the Z (cis) and the E (trans) isomers, respectively, of \((6^R,7^R)-7-[(R)-2-amino-2-(p-hydroxyphenyl)acetamido]8-oxo-3-propenyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms nor more than 1,050 micrograms of cefprozil activity per milligram, on an anhydrous basis.

(ii) The ratio of its (E) isomer to total cefprozil is not less than 0.06 nor more than 0.11.

(iii) Its moisture content is not less than 3.5 percent nor more than 6.5 percent.

(iv) The pH of an aqueous solution containing 5 milligrams per milliliter is not less than 3.5 nor more than 6.5.

(v) It is crystalline.
§ 442.80

(vi) It gives positive identity tests.

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefprozil potency, E isomer to total cefprozil ratio, moisture, pH, crystallinity, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 280 nanometers, a 25 centimeter × 3.9 to 4.6 millimeter (id) column packed with microparticulate (5 to 10 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded to silicas, a flow rate of 1.0 milliliter per minute, and a known injection volume of 10 microliters. The retention time for cefprozil (Z) is between 4 and 6 minutes and the retention time for cefprozil (E) is between 6 and 8 minutes. Mobile phase, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) Mobile phase. Dissolve 20.7 grams of ammonium phosphate, monobasic in 1,800 milliliters of water and adjust the pH to 4.4 with phosphoric acid, if necessary. Add 200 milliliters of acetonitrile and mix. Filter the mobile phase through a suitable filter capable of removing particulate matter 0.5 micron in diameter and degas it just prior to its introduction into the chromatograph. The proportion of acetonitrile may be modified in the range of 6 to 14 percent to obtain the desired retention times. Increasing the amount of acetonitrile will decrease both the retention times and the separation between the isomers, whereas, decreasing the amount of acetonitrile will increase retention times and the separation between the isomers.

(ii) Preparation of working standard solutions—(A) Cefprozil (Z) working standard solution. Accurately weigh approximately 12.5 milligrams of the cefprozil (Z) working standard into a 50-milliliter volumetric flask. Dilute to volume with water and shake the flask vigorously until the solute dissolves completely. Use this solution within 6 hours.

(B) Cefprozil (E) working standard solution. Accurately weigh approximately 12.5 milligrams of the cefprozil (E) working standard into a 50-milliliter volumetric flask. Dilute to volume with water and shake the flask vigorously until the solute dissolves completely. Pipet 5 milliliters into a 50-milliliter volumetric flask, dilute to volume with water and mix thoroughly. Use this solution within 6 hours.

(iii) Sample solution. Accurately weigh approximately 15 milligrams of sample into a 50-milliliter volumetric flask. Dilute to volume with water and shake the flask vigorously until the solute dissolves completely. Use this solution within 6 hours.

(iv) System suitability requirements—(A) Asymmetry factor. The asymmetry factor (A_S) is satisfactory if it is not less than 0.9 and not more than 1.1 for the cefprozil (Z) response.

(B) Efficiency of the column. The absolute efficiency (h_r) is satisfactory if it is not more than 10 for the cefprozil (Z) response.

(C) Resolution factor. The resolution factor (R) between the response for cefprozil (Z) and the response for cefprozil (E) is satisfactory if it is not less than 2.5.

(D) Coefficient of variation (Relative standard deviation). The coefficient of variation (S_d of 5 replicate injections of the cefprozil (Z) reference solution response) is satisfactory if it is not more than 2.0 percent.

(E) Capacity factor (k'). The capacity factor (k') for cefprozil (Z) is satisfactory if it is not less than 0.7 and not more than 1.1. If the system suitability parameters have been met, then proceed as described in § 436.216(b) of this chapter.

(v) Calculations. Calculate the micrograms of cefprozil per milligram of sample on an anhydrous basis as follows:
Micrograms of cefprozil (Z) or cefprozil (E) per milligram (as is) = \frac{A_u \times P}{A_i \times C_u}

Micrograms of cefprozil per milligram (as is) = \frac{\text{cefprozil (Z)}}{\text{cefprozil (E) potency}}

Micrograms of cefprozil per milligram (Anhydrous) = \frac{(as is) \times 100}{(100 - m)}

where:
- $A_u$ = Area of the cefprozil (Z) or cefprozil (E) response in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- $A_i$ = Area of the cefprozil (Z) or cefprozil (E) response in the chromatogram of the cefprozil (Z) or the cefprozil (E) working standard;
- $P_s$ = Cefprozil (Z) or cefprozil (E) activity in the cefprozil (Z) or the cefprozil (E) working standard solution in micrograms per milliliter;
- $C_u$ = Milligrams of sample per milliliter of sample solution; and
- $m$ = Percent moisture content of the sample.

(2) Cefprozil (E)/cefprozil ratio. Using the procedure described in paragraph (b)(1) of this section calculate the cefprozil (E)/cefprozil ratio as follows:

Trans ratio = \frac{\text{cefprozil (E) (mcg/mg, as is)}}{\text{cefprozil (mcg/mg, as is) Total}}

(3) Moisture. Proceed as directed in §436.201 of this chapter.

(4) pH. Proceed as directed in §436.202 of this chapter, using a carbon dioxide free aqueous solution containing 5 milligrams of cefprozil per milliliter.

(5) Crystallinity. Proceed as directed in §436.203(a) of this chapter.

(6) Identity—(i) Infrared. Proceed as directed in §436.211 of this chapter, using a 1.0 percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

(ii) High performance liquid chromatography (HPLC). The HPLC retention times for the responses of the cefprozil isomers in the assay preparation of the sample must be within 2 percent of the HPLC retention times of the responses of the corresponding cefprozil working standards.

[58 FR 26660, May 4, 1993]
§ 442.104b Cefaclor monohydrate for oral suspension.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefaclor monohydrate for oral suspension is cefaclor monohydrate with one or more suitable and harmless diluents, buffer substances, colorings and flavorings. When reconstituted as directed in the labeling, each milliliter contains cefaclor monohydrate equivalent to 25 milligrams, 37.5 milligrams, 50 milligrams, or 75 milligrams of cefaclor. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefaclor that it is represented to contain. Its moisture content is not more than 2.0 percent. When reconstituted as directed in the labeling, its pH is not less than 2.5 and not more than 5.0. The cefaclor monohydrate used conforms to the standards prescribed by §442.4(a)(1).

(ii) Preparation of sample solution. Place one capsule into a high-speed glass blender jar containing sufficient 0.1M potassium phosphate buffer, pH 4.5 (as described in §436.101(a)(4) of this chapter) to obtain a concentration of 1 milligram of cefaclor per milliliter. Filter a portion to be used through a 10-micron filter.

(iii) Calculations. Calculate the cefaclor content in milligrams per capsule as follows:

\[
\text{Milligrams of cefaclor per capsule} = \frac{A_u \times P_a \times d}{A_s \times 1,000}
\]

where:
- \(A_u\) = Absorbance of sample solution;
- \(P_a\) = Potency of working standard in micrograms per milliliter;
- \(A_s\) = Absorbance of working standard solution;
- \(d\) = Dilution factor of the sample.

(b) The batch. A minimum of six immediate containers.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

§ 442.104b Cefaclor monohydrate for oral suspension.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefaclor monohydrate for oral suspension is cefaclor monohydrate with one or more suitable and harmless diluents, buffer substances, colorings and flavorings. When reconstituted as directed in the labeling, each milliliter contains cefaclor monohydrate equivalent to 25 milligrams, 37.5 milligrams, 50 milligrams, or 75 milligrams of cefaclor. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefaclor that it is represented to contain. Its moisture content is not more than 2.0 percent. When reconstituted as directed in the labeling, its pH is not less than 2.5 and not more than 5.0. The cefaclor monohydrate used conforms to the standards prescribed by §442.4(a)(1).

(ii) Preparation of sample solution. Reconstitute the sample as directed in the labeling. Transfer a 5.0-milliliter portion into an appropriate-sized volumetric flask and dilute to volume with 0.1M potassium phosphate buffer, pH 4.5 (as described in §436.101(a)(4) of this chapter) to obtain a concentration of 1 milligram of cefaclor per milliliter.

(iii) Calculations. Calculate the cefaclor content as follows:

\[
\text{Milligrams of cefaclor for 5 milliliters of sample} = \frac{A_u \times P_a \times d}{A_s \times 1,000}
\]

where:
- \(A_u\) = Absorbance of sample solution;
- \(P_a\) = Potency of working standard in micrograms per milliliter;
- \(A_s\) = Absorbance of working standard solution;
- \(d\) = Dilution factor of the sample.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using the drug reconstituted as directed in the labeling.

§ 442.106 Cefadroxil monohydrate oral dosage forms.

§ 442.106a Cefadroxil monohydrate capsules.
(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefadroxil monohydrate capsules are composed of cefadroxil monohydrate and one or more suitable and harmless lubricants and diluents enclosed in a gelatin capsule. Each capsule contains either 250 or 500 milligrams of cefadroxil. Its moisture content is not more than 7.0 percent. The cefadroxil monohydrate used conforms to the standards prescribed by § 442.6(a)(1).
(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.
(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:
(i) Results of tests and assays on:
(a) The cefadroxil monohydrate used in making the batch for potency, moisture, pH, absorptivity, identity, and crystallinity.
(b) The batch for potency and moisture.
(ii) Samples required:
(a) The cefadroxil monohydrate used in making the batch: 10 packages, each containing approximately 500 milligrams.
(b) The batch: A minimum of 30 capsules.
(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.
(i) Microbiological agar diffusion assay. Proceed as directed in § 442.106b of this chapter, preparing the sample as follows: Place a representative number of capsules in a high-speed glass blender jar containing sufficient distilled water to give a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to a concentration of 1 milligram of cefadroxil per milliliter (estimated).
(2) Moisture. Proceed as directed in § 436.201 of this chapter.


§ 442.106b Cefadroxil monohydrate tablets.
(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefadroxil monohydrate tablets are composed of cefadroxil monohydrate and one or more suitable and harmless binders and lubricants, and with or without coloring and film-coating substances. Each tablet contains cefadroxil monohydrate equivalent to 1,000 milligrams of cefadroxil. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefadroxil that it is represented to contain. Its moisture content is not more than 8.0 percent. The tablets disintegrate within 15 minutes. The cefadroxil monohydrate used conforms to the standards prescribed by § 442.6(a)(1).
(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.
(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:
(i) Results of tests and assays on:
(a) The cefadroxil monohydrate used in making the batch for potency, moisture, pH, absorptivity, identity, and crystallinity.
(b) The batch for potency, moisture, and disintegration time.
(ii) Samples required:
(a) The cefadroxil monohydrate used in making the batch: 10 packages, each
§ 442.106c

containing approximately 500 milligrams.

(b) The batch: A minimum of 36 tablets.

(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to obtain a stock solution of convenient concentration. Blend for 3 to 5 minutes. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 20 micrograms of cefadroxil per milliliter (estimated).

(ii) Hydroxylamine colorimetric assay. Proceed as directed in § 442.40(b)(1)(ii) of this chapter, except prepare the working standard and sample solutions and calculate the cefadroxil content as follows:

(a) Preparation of working standard solution. Dissolve and dilute an accurately weighed portion of the cefadroxil working standard in sufficient distilled water to a final concentration of 1 milligram of cefadroxil per milliliter.

(b) Preparation of sample solution. Blend a representative number of tablets in a high-speed glass blender jar with sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to a concentration of 1 milligram of cefadroxil per milliliter (estimated).

(c) Calculations. Calculate the cefadroxil content as follows:

\[
\text{Milligrams per tablet} = \frac{A_u \times P_s \times d}{A_s \times 1,000 \times n}
\]

where:

\(A_u\) = Absorbance of sample solution;

\(P_s\) = Potency of working standard in micrograms per milligram;

\(d\) = Dilution factor for sample;

\(A_s\) = Absorbance of working standard solution;

\(n\) = Number of tablets in the sample assayed.

(2) Moisture. Proceed as directed in § 436.201 of this chapter.

(3) Disintegration time. Proceed as directed in § 436.212 of this chapter, using the procedure described in paragraph (e)(1) of that section.

§ 442.106c Cefadroxil monohydrate for oral suspension.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefadroxil monohydrate for oral suspension is cefadroxil monohydrate with one or more suitable and harmless preservatives, suspending agents, surfactants, binders, and flavorings. When reconstituted as directed in the labeling, each milliliter contains cefadroxil monohydrate equivalent to either 25, 50, or 100 milligrams of cefadroxil. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefadroxil that it is represented to contain. Its moisture content is not more than 2.0 percent. When reconstituted as directed in the labeling, its pH is not less than 4.5 and not more than 6.0. The cefadroxil monohydrate used conforms to the standards prescribed by § 442.6(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cefadroxil monohydrate used in making the batch for potency, moisture, pH, absorbity, identity, and crystallinity.

(b) The batch for potency, moisture, and pH.

(ii) Samples required:

(a) The cefadroxil monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of six immediate containers.

(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from
the hydroxylamine colorimetric assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the sample as directed in the labeling. Transfer an accurately measured representative portion of the suspension into an appropriate-sized volumetric flask and dilute to volume with 1 percent potassium phosphate buffer, pH 6.0 (solution 1). Further dilute an aliquot of this solution with solution 1 to the reference concentration of 20.0 micrograms of cefadroxil per milliliter (estimated).

(ii) Hydroxylamine colorimetric assay. Proceed as directed in §442.40(b)(1)(ii) of this chapter, except prepare the working standard and sample solutions and calculate the cefadroxil content as follows:

(a) Preparation of working standard solution. Dissolve and dilute an accurately weighed portion of the cefadroxil working standard in sufficient distilled water to a final concentration of 1 milligram of cefadroxil per milliliter.

(b) Preparation of sample solution. Reconstitute the sample as directed in the labeling. Transfer an accurately measured representative portion to a volumetric flask and bring to volume with distilled water to give a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to a concentration of 1 milligram of cefadroxil per milliliter (estimated).

(c) Calculations. Calculate the cefadroxil content as follows:

\[
\text{Milligrams per dose} = \frac{A_s \times P_s \times d}{A_u \times 1,000}
\]

where:
- \(A_u\) = Absorbance of sample solution;
- \(P_s\) = Potency of working standard in micrograms per milligram;
- \(d\) = Dilution factor for sample;
- \(A_s\) = Absorbance of working standard solution.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using the drug reconstituted as directed in the labeling.

§ 442.107b Cefadroxil hemihydrate tablets.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefadroxil hemihydrate tablets are composed of cefadroxil hemihydrate and one or more suitable and harmless binders and lubricants, with or without coloring and film-coating substances. Each tablet contains cefadroxil hemihydrate equivalent to 1,000 milligrams of cefadroxil. Its cefadroxil content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefadroxil that it is represented to contain. Its moisture content is not more than 8.0 percent. It passes the dissolution test. The cefadroxil hemihydrate used conforms to the standards prescribed in §442.7(a)(1).

(b) Tests and methods of assay—(1) Cefadroxil content. Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 1 to the reference concentration of 20 micrograms of cefadroxil per milliliter (estimated).
Hydroxylamine colorimetric assay for cefadroxil. Proceed as directed in §442.40(b)(1)(ii), except prepare the working standard and sample solutions and calculate the potency of the sample as follows:

(A) Preparation of working standard solutions. Dissolve and dilute an accurately weighed portion of the cefadroxil working standard in sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to a concentration of 1 milligram of cefadroxil per milliliter.

(B) Preparation of sample solutions. Blend a representative number of tablets in a high-speed glass blender jar with sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to a concentration of 1 milligram of cefadroxil per milliliter.

(C) Calculations. Calculate the cefadroxil content as follows:

\[
\text{Milligrams of cefadroxil per tablet} = \frac{A_s \times P_s \times d}{A_u \times 1,000 \times n}
\]

where:
- \(A_s\) = Absorbance of sample solution;
- \(A_u\) = Absorbance of working standard solution;
- \(P_s\) = Potency of working standard solution in micrograms per milliliter;
- \(d\) = Dilution factor of the sample; and
- \(n\) = Number of tablets in the sample assayed.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) Dissolution. Proceed as directed in §436.215 of this chapter. The quantity Q (the amount of cefadroxil dissolved) is 75 percent within 30 minutes.

[59 FR 8857, Feb. 24, 1994]

§ 442.115 Cefixime trihydrate oral dosage forms.

§ 442.115a Cefixime trihydrate for oral suspension.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefixime trihydrate for oral suspension is cefixime trihydrate with one or more suitable and harmless preservatives, suspending agents, diluents, and flavorings. When reconstituted as directed in the labeling, each milliliter contains the equivalent of 20 milligrams of cefixime. Its cefixime trihydrate potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefixime that it is represented to contain. Its moisture content is not more than 2.0 percent. When reconstituted as described in labeling, the pH of the suspension is not less than 2.5 and not more than 4.5. It passes the identity test for the presence of the cefixime moiety. The cefixime trihydrate used conforms to the standards prescribed by §442.15(a)(1) of this part.

(2) Labeling. It shall be labeled in accordance with the requirements of §436.5 of this chapter.

(b) Tests and methods of assay—(1) Content. Proceed as directed in §442.15(b)(1) of this part, preparing the sample solution and calculating the cefixime content as follows:

(i) Preparation of the sample solution. Reconstitute as directed in the labeling. Transfer a 5.0-milliliter portion of the suspension into an appropriately sized volumetric flask and quantitatively dilute stepwise with 0.1M phosphate buffer, pH 7.0, to obtain a concentration of 0.2 milligram of cefixime activity per milliliter.

(ii) Calculations. Calculate the cefixime content as follows:

\[
\text{Milligrams of cefixime per 5 milliliters of sample} = \frac{A_u \times P_s \times d}{A_u \times 1,000}
\]

where:
§ 442.115b

A = Area of the cefixime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
A = Area of the cefixime peak in the chromatogram of the cefixime working standard.
P = Cefixime activity in the cefixime working standard solution in micrograms per milliliter; and

d = Dilution factor of the sample.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using the drug reconstituted as directed in the labeling.

(4) Identity. The high performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section, compares qualitatively to that of the cefixime working standard.

[53 FR 24259, June 28, 1988]

§ 442.115b Cefixime trihydrate tablets.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefixime trihydrate tablets are composed of cefixime trihydrate and one or more suitable and harmless diluents, binders, lubricants, colorings, and coating substances. Each tablet contains cefixime trihydrate equivalent to either 200 milligrams or 400 milligrams of cefixime. Its cefixime trihydrate content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of cefixime that it is represented to contain. Its moisture content is not more than 10.0 percent. It passes the dissolution test. It passes the identity test for the presence of the cefixime moiety. The cefixime used conforms to the standards prescribed by §442.15(a)(1) of this part.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:
(A) The cefixime used in making the batch for potency, moisture, dissolution, and identity.
(B) The batch, for content, moisture, dissolution, and identity.
(ii) Samples, if required by the Director, Center for Drug Evaluation and Research.

(A) The cefixime used in making the batch: 10 packages, each containing approximately 500 milligrams.
(B) The batch: A minimum of 10 immediate containers.

(b) Tests and methods of assay—(1) Content. Proceed as directed in §442.15(b)(1) of this part, preparing the sample solution and calculating the cefixime content as follows:

(i) Preparation of sample solution. Grind one or a known number of tablets using a mortar and pestle. Quantitatively transfer the ground tablet(s) into a suitable volumetric flask, sonicate and dilute with 0.1M phosphate buffer, pH 7.0 to a concentration of 4 milligrams per milliliter. Centrifuge the sample at 3,000 revolutions per minute for 10 minutes. Take an aliquot of the supernatant and qualitatively dilute to a concentration of 0.2 milligram of cefixime activity per milliliter in 0.1M phosphate buffer, pH 7.0 (estimated).

(ii) Calculations. Calculate the cefixime content as follows:

\[
\text{Milligrams of cefixime per tablet} = \frac{A_u \times P_s \times d}{A_s} \times n
\]

where:
A = Area of the cefixime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
A = Area of the cefixime peak in the chromatogram of the cefixime working standard.
P = Cefixime activity in the cefixime working standard solution in micrograms per milliliter;
d = Dilution factor of the sample; and
n = Number of tablets in the sample.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) Dissolution test. Proceed as directed in §436.215 of this chapter. The quantity Q (the amount of cefixime dissolved) is 75 percent within 45 minutes.

(4) Identity. The high-performance liquid chromatogram of the sample determined as directed in paragraph
Food and Drug Administration, HHS

§ 442.119a Cefuroxime axetil tablets.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefuroxime axetil tablets are composed of cefuroxime axetil and one or more suitable and harmless diluents, binders, lubricants, and colorings. Each tablet contains 125 milligrams, 250 milligrams, or 500 milligrams of cefuroxime activity. Its potency is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of cefuroxime activity that it is represented to contain. Its moisture content is not more than 2.0 percent at the time of certification and not more than 6.0 percent at the time of expiry. It passes the dissolution test. It passes the film-coat rupture test. It passes the identity test. The cefuroxime axetil used conforms to the standards prescribed by § 442.19(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:
   (A) The cefuroxime axetil used in making the batch for potency, isomer A ratio, moisture, crystallinity, and identity.
   (B) The batch for potency, moisture, dissolution, film-coat rupture, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:
   (A) The cefuroxime axetil used in making the batch: 10 packages, each containing approximately 500 milligrams.
   (B) The batch: A minimum of 100 tablets.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in § 442.19(b)(1). Working standard and sample solutions, system suitability requirements, and calculations are as follows:

   (i) Preparation of working standard and sample solutions—(A) Working standard solution. Dissolve approximately 30 milligrams of the cefuroxime axetil working standard, accurately weighed, in methanol and dilute to 25 milliliters. Transfer 10.0 milliliters of the working standard solution to a 50-milliliter volumetric flask. Add 5.0 milliliters of internal standard solution, 3.8 milliliters of methanol, and dilute to volume with 0.2M ammonium phosphate solution to obtain a stock solution containing 0.24 milligram of cefuroxime axetil per milliliter. Store the stock solution under refrigeration no more than 8 hours.
   (B) Sample solution. Grind a representative number of tablets in a mortar and pestle. Immediately swirl the ground tablets in a volumetric flask containing methanol and shake for 10 minutes to dissolve the ground cefuroxime axetil. Dilute with methanol to give a stock solution of convenient concentration. Filter the stock solution. Transfer 5.0 milliliters of filtrate to a 50-milliliter volumetric flask. Add 5.0 milliliters of internal standard solution and 8.8 milliliters of methanol. Dilute to volume with 0.2M ammonium phosphate solution. Store in a refrigerator and use within 8 hours.

   (ii) System suitability requirements—(A) Tailing factor. The tailing factor (T) is satisfactory for isomer A if it is not more than 1.5 at 5 percent of peak height.
   (B) Efficiency of the column. The efficiency of the column (n) is satisfactory for isomer A if it is greater than 3,000 theoretical plates.
   (C) Resolution. The resolution (R) between isomer A and isomer B of cefuroxime axetil is satisfactory if it is not less than 1.5 and the resolution (R) between isomer A and the delta-2 isomers of cefuroxime axetil is satisfactory if it is not less than 1.5.
   (D) Coefficient of variation. The coefficient of variation (S_u in percent) of five replicate injections is not more than 2.0 percent. If the system suitability requirements have been met, then proceed as described in § 436.209(b) of this chapter. Alternate chromatographic
§ 442.119b Cefuroxime axetil for oral suspension.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefuroxime axetil for oral suspension is cefuroxime axetil with one or more suitable and harmless diluents, suspending and sweetening agents, and flavorings. When reconstituted as directed in the labeling, it contains cefuroxime axetil equivalent to 25 milligrams of cefuroxime per milliliter. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cefuroxime that it is represented to contain. It passes the dissolution test. Its moisture content is not more than 0.2 percent. When reconstituted as directed in the labeling, its pH is not less than 3.5 and not more than 5.5. It passes the identity test. The cefuroxime axetil used conforms to the standards prescribed by § 442.19(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in § 442.19(b)(1). Working standard and sample solutions and calculations are as follows:

(i) Preparation of working standard solution. Dissolve approximately 15 milligrams of the cefuroxime axetil working standard, accurately weighed, in 20.0 milliliters of methanol in a 50-milliliter volumetric flask. Dilute to volume with deionized water, and swirl to mix. Store for no more than 8 hours under refrigeration and protected from light.

(ii) Preparation of sample solution. Reconstitute the sample as directed in the labeling. Transfer an accurately measured representative portion of the suspension equivalent to one dose into a 200-milliliter volumetric flask. Add 10 milliliters of methanol and disperse

(iv) Calculations. Calculate the cefuroxime content as follows:

\[ \text{Milligrams of cefuroxime per tablet} = \frac{R_u \times P_s \times d}{R_s \times n} \]

where:

- \( R_u \) = Sum of the peak heights of the cefuroxime axetil sample isomer A and isomer B peaks/Peak height of the internal standard;
- \( R_s \) = Sum of the peak heights of the cefuroxime axetil working standard isomer A and isomer B peaks/Peak height of the internal standard;
- \( P_s \) = Potency of the cefuroxime axetil working standard in milligrams of cefuroxime activity per milliliter;
- \( d \) = Dilution factor of the sample; and
- \( n \) = Number of tablets in the sample assayed.

(2) Moisture. Proceed as directed in § 436.201 of this chapter, using the titration procedure described in paragraph (e)(1) of that section.

(3) Dissolution. Proceed as directed in § 436.215 of this chapter. The quantity \( Q \) (the amount of cefuroxime activity dissolved) is 60 percent at 15 minutes and 75 percent at 45 minutes.

(4) Film-coat rupture test. Proceed as directed in § 436.217 of this chapter.

(5) Identity. The high-performance liquid chromatogram of the sample solution determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cefuroxime axetil working standard solution.

the sample. Dilute to volume with methanol. Dilute 20.0 milliliters of this solution to volume in a 50-milliliter volumetric flask with deionized water, swirl to mix, and allow to stand for 10 minutes. (Note: A white turbidity is formed.) Filter this solution via a suitable disposable filter unit, discarding the first 5 milliliters. Store for no more than 8 hours under refrigeration and protect from light.

(iii) Calculations. Calculate the milligrams of cefuroxime per dose (5 milliliters) as follows:

$$\text{Milligrams of cefuroxime} = \frac{A_U \times P_S \times d}{A_S \times 1,000}$$

where:

- $A_U$ = Sum of the areas of the cefuroxime axetil sample isomer A and isomer B peaks;
- $A_S$ = Sum of the peak areas of the cefuroxime axetil working standard isomer A and isomer B peaks;
- $P_S$ = Cefuroxime activity in the cefuroxime axetil working standard solution in micrograms per milliliter; and
- $d$ = Dilution factor of the sample.

(2) Dissolution. Proceed as directed in §436.215 of this chapter. The quantity Q (the amount of cefuroxime activity dissolved) is 60 percent at 30 minutes.

(3) Moisture. Proceed as directed in §436.201 of this chapter.

(4) pH. Reconstitute as directed in the labeling and proceed as directed in §436.202 of this chapter.

(5) Identity. The high-performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cefuroxime axetil working standard.

[60 FR 27222, May 23, 1995]

§ 442.121b Cefaloglycin dihydrate oral dosage forms.

§ 442.121a Cefaloglycin dihydrate capsules.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefaloglycin dihydrate capsules are composed of cefaloglycin dihydrate and one or more suitable lubricants and diluents enclosed in a gelatin capsule. Each capsule contains cefaloglycin dihydrate equivalent to 250 milligrams of cefaloglycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefaloglycin that it is represented to contain. Its moisture content is not more than 9 percent. The cefaloglycin used conforms to the standards prescribed by §442.21(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cefaloglycin dihydrate used in making the batch for potency, moisture, pH, cefaloglycin content, identity, and crystallinity.

(b) The batch for potency and moisture.

(ii) Samples required:

(a) The cefaloglycin dihydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of 30 capsules.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar with sufficient 0.1 M potassium phosphate buffer, pH 4.5 (solution 4), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 4 to the reference concentration of 10 micrograms of cefaloglycin per milliliter (estimated).

(2) Moisture. Proceed as directed in §436.201 of this chapter.


§ 442.121b Cefaloglycin dihydrate for oral suspension.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefaloglycin dihydrate for oral suspension is cefaloglycin dihydrate with one or more suitable diluents, buffer substances, colorings, and flavorings. When reconstituted as directed in the labeling, each milliliter contains cefaloglycin dihydrate...
§ 442.127 Cephalexin monohydrate oral dosage forms.

(a) Requirements for certification—

(1) Standards of identity, strength, quality, and purity. Cephalexin monohydrate tablets are composed of cephalexin monohydrate and one or more suitable and harmless diluents, binders, lubricants, colorings, and coating substances. Each tablet contains cephalexin monohydrate equivalent to 250, 500, or 1,000 milligrams of cephalexin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cephalexin that it is represented to contain. Its moisture content is not more than 9 percent. The tablets disintegrate within 30 minutes. The cephalexin monohydrate used conforms to the standards prescribed by §442.27(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cephalexin monohydrate used in making the batch for potency, moisture, pH, cephalexin content, identity, and crystallinity.

(b) The batch for potency, moisture, pH, and identity.

(ii) Samples required:

(a) The cephalexin monohydrate used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch: A minimum of six immediate containers.

(b) Tests and methods of assay—

(1) Potency. Proceed as directed in §436.106 of this chapter, preparing the sample for assay as follows: Reconstitute as directed in the labeling. Place an accurately measured representative portion of the suspension into an appropriately sized volumetric flask and dilute to volume with 0.1M potassium phosphate buffer, pH 4.5 (solution 4). Further dilute an aliquot of the stock solution with solution 4 to the reference concentration of 10 micrograms of cephalexin per milliliter (estimated). Shake vigorously on a mechanical shaker for 30 minutes. Filter through Whatman No. 1 filter paper, discarding the first few milliliters of filtrate. Further dilute an aliquot of the filtrate with sufficient distilled water to give a concentration of 0.05 milligram of cephalexin per milliliter (estimated). Using a suitable spectrophotometer, record the ultraviolet absorption spectrum of this solution from 230 to 320 nanometers. The spectrum compares qualitatively to that of the cephalexin working standard similarly treated.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using the drug reconstituted as directed in the labeling.

(4) Identity. Dilute a representative portion of the sample with sufficient distilled water to give a concentration of 2.5 milligrams of cephalexin per milliliter (estimated). Shake vigorously on a mechanical shaker for 30 minutes. Filter through Whatman No. 1 filter paper, discarding the first few milliliters of filtrate. Further dilute an aliquot of the filtrate with sufficient distilled water to give a concentration of 0.05 milligram of cephalexin per milliliter (estimated). Using a suitable spectrophotometer, record the ultraviolet absorption spectrum of this solution from 230 to 320 nanometers. The spectrum compares qualitatively to that of the cephalexin working standard similarly treated.

§ 442.127b Cephalexin monohydrate capsules.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephalexin monohydrate capsules are composed of cephalexin monohydrate and one or more suitable and harmless lubricants and diluents enclosed in a gelatin capsule. Each capsule contains cephalexin monohydrate equivalent to either 125, 250, or 500 milligrams of cephalexin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cephalexin that it is represented to contain. Its moisture content is not more than 10 percent. The cephalexin monohydrate used conforms to the standards prescribed by §442.27(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cephalexin monohydrate used in making the batch for potency, moisture, pH, absorptivity, identity, and crystallinity.

(b) The batch for potency and moisture.

(ii) Samples required:

(a) The cephalexin monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of 36 tablets.

(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Further dilute with solution 1 to the reference concentration of 20.0 micrograms of cephalexin per milliliter (estimated).

(ii) Iodometric assay. Proceed as directed in §436.204 of this chapter, preparing the sample as follows: Blend a representative number of tablets in a high-speed glass blender with sufficient distilled water to give a stock solution of convenient concentration. Further dilute with distilled water to the prescribed concentration of cephalexin.

Note: The 10.0 milliliters of 0.01N iodine must be added within 20 seconds after the addition of the 2.0 milliliters of 1.2N hydrochloric acid, and the assay should be completed within 1 hour after the sample and standard are first put into solution.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) Disintegration time. Proceed as directed in §436.212 of this chapter, using the procedure described in paragraph (e)(1) of that section.

§ 442.127c  Cephalexin monohydrate for oral suspension.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephalexin monohydrate for oral suspension is cephalexin monohydrate with one or more suitable and harmless diluents, buffer substances, colorings, and flavorings. When reconstituted as directed in the labeling, each milliliter contains cephalexin monohydrate equivalent to 25 milligrams, 50 milligrams, or 100 milligrams of cephalexin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cephalexin that it is represented to contain. Its moisture content is not more than 2 percent. When reconstituted as directed in the labeling, its pH is not less than 3.0 and not more than 6.0. The cephalexin used conforms to the standards prescribed by §442.27(a)(1).

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the sample as directed in the labeling. Transfer an accurately measured representative portion of the suspension into an appropriate-sized volumetric flask and dilute to volume with 1-percent potassium phosphate buffer, pH 6.0 (solution 1). Further dilute an aliquot of this solution with solution 1 to the reference concentration of 20.0 micrograms of cephalexin per milliliter (estimated).

(ii) Iodometric assay. Proceed as directed in §436.204 of this chapter, preparing the sample as follows: Reconstitute the sample as directed in the labeling. Transfer an accurately measured representative portion to a volumetric flask and bring to volume with distilled water. Further dilute an aliquot of this solution with distilled water to the prescribed concentration of cephalexin.

NOTE: The 10 milliliters of 0.01N iodine must be added within 20 seconds after the addition of the 2.0 milliliters of 1.2N hydrochloric acid, and the assay should be completed within 1 hour after the sample and standard are first put into solution.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

§ 442.128  Cephalexin hydrochloride monohydrate tablets.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephalexin hydrochloride monohydrate tablets are composed of cephalexin hydrochloride monohydrate and one or more suitable and harmless lubricants, colorings and coating substances. Each tablet contains cephalexin hydrochloride monohydrate equivalent to 250 milligrams, 333 milligrams or 500 milligrams of cephalexin. Its cephalexin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cephalexin that it is represented to contain.
milligrams of cephalaxin that it is represented to contain. Its moisture content is not more than 8.0 percent. The tablets pass the dissolution test. It passes the identity test. The cephalaxin hydrochloride monohydrate used conforms to the standards prescribed by §442.28(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:
(A) The cephalaxin hydrochloride monohydrate used in making the batch for cephalaxin potency, moisture, pH, identity, and crystallinity.
(B) The batch for cephalaxin content, moisture, dissolution, and identity.
(ii) Samples, if required by the Director, Center for Drug Evaluation and Research.
(A) The cephalaxin hydrochloride monohydrate used in making the batch: 10 packages, each containing approximately 500 milligrams.
(B) The batch: A minimum of 36 tablets.

(b) Tests and methods of assay—
(1) Cephalexin content. Proceed as directed in §442.140c(b)(1)(ii), except that “cephalexin” is substituted at each occurrence of “cephradine”.
(2) Moisture. Proceed as directed in §436.201 of this chapter.
(3) Dissolution. Proceed as directed in §436.215 of this chapter. The quantity Q (the amount of cephalaxin dissolved) is not less than 75 percent at 45 minutes.
(4) Identity. Proceed as directed in §436.367 of this chapter.

[54 FR 48860, Nov. 28, 1989]
distilled water to 1 milligram of cephradine per milliliter (estimated).

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using the drug reconstituted as directed in the labeling.

§ 442.140b Cephradine capsules.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephradine capsules are composed of cephradine and one or more suitable and harmless lubricants and diluents enclosed in a gelatin capsule. Each capsule contains 250 milligrams or 500 milligrams of cephradine. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cephradine that it is represented to contain. Its loss on drying is not more than 7.0 percent. The cephradine used conforms to the standards prescribed by §442.40(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cephradine used in making the batch for potency, moisture, pH, cephalaxin content, identity, and crystallinity.

(b) The batch for potency and loss on drying.

(ii) Samples required:

(a) The cephradine used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch: A minimum of 30 capsules.

(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 1 to the reference concentration of 10.0 micrograms of cephradine per milliliter (estimated).

(ii) Hydroxylamine colorimetric assay. Proceed as directed in §442.40(b)(1)(ii) of this chapter, preparing the sample as follows: Blend a representative number of capsules in a high-speed glass blender jar with sufficient distilled water to give a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to 1 milligrams of cephradine per milliliter (estimated).

(2) Loss on drying. Proceed as directed in §436.200(b) of this chapter.

[40 FR 26272, June 23, 1975, as amended at 50 FR 19919, May 13, 1985]

§ 442.140c Cephradine tablets.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephradine tablets are composed of cephradine and one or more suitable and harmless diluents, binders, lubricants, and colorings. Each tablet contains 1,000 milligrams of cephradine. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cephradine that it is represented to contain. Its moisture content is not more than 6.0 percent. It disintegrates within 30 minutes. The cephradine used conforms to the standards prescribed by §442.40(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cephradine used in making the batch for potency, moisture, pH, cephalaxin content, identity, and crystallinity.

(b) The batch for potency, moisture, and disintegration time.

(ii) Samples required:

(a) The cephradine used in making the batch: 10 packages, each containing approximately 500 milligrams.
Food and Drug Administration, HHS

§ 442.141 Cephradine dihydrate capsules.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephradine dihydrate capsules are composed of cephradine dihydrate and one or more suitable and harmless lubricants and diluents enclosed in a gelatin capsule. Each capsule contains 250 milligrams or 500 milligrams of cephradine. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cephradine that it is represented to contain. Its moisture content is not more than 11.0 percent. It passes the dissolution test if the quantity \( Q \) is 85 percent at 60 minutes. The cephradine dihydrate used conforms to the standards prescribed by §442.41(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cephradine dihydrate used in making the batch for potency, moisture, pH, cephalexin content, identity, and crystallinity.

(b) The batch for potency, moisture, and dissolution.

(ii) Samples required:

(a) The cephradine dihydrate used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch: A minimum of 100 capsules.

(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 1 to the reference concentration of 10.0 micrograms of cephradine per milliliter (estimated).

(ii) Hydroxylamine colorimetric assay. Proceed as directed in §442.40(b)(1)(ii), except prepare the sample and calculate the cephradine content as follows:

(a) Preparation of sample. Blend a representative number of capsules in a high-speed glass blender jar with sufficient distilled water to give a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to 1 milligram of cephradine per milliliter (estimated).

(b) Calculations. Calculate the cephradine content as follows:

\[
\text{Milligrams per tablet} = \frac{A_u \times P_s \times d \times A_s \times 1,000 \times n}{A_t \times 1,000 \times n}
\]

where:

- \( A_u \) = Absorbance of sample solution;
- \( P_s \) = Potency of working standard in micrograms per milligram;
- \( d \) = Dilution factor for sample;
- \( A_s \) = Absorbance of working standard solution;
- \( n \) = Number of tablets in the sample assayed.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) Disintegration time. Proceed as directed in §436.212 of this chapter, using the procedure described in paragraph (e)(1) of that section.

10.0 micrograms of cephradine per milliliter (estimated).

(ii) Hydroxylamine colorimetric assay. Proceed as directed in §442.40(b)(1)(ii), except prepare the sample solution and calculate the cephradine content as follows:

(a) Preparation of sample solution. Blend a representative number of capsules in a high-speed glass blender jar with sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of this solution with distilled water to a concentration of 1 milligram of cephradine per milliliter (estimated).

(b) Calculations. Calculate the cephradine content as follows:

\[
\text{Milligrams per capsule} = \frac{A_s \times P \times d}{A_w \times 1,000 \times n}
\]

where:

- \(A_s\) = Absorbance of sample solution;
- \(P_s\) = Potency of working standard in micrograms per milligram;
- \(d\) = Dilution factor for sample;
- \(A_w\) = Absorbance of working standard solution;
- \(n\) = Number of capsules in the sample assayed.

(2) Moisture. Proceed as directed in §436.201 of this chapter.

(3) Dissolution. Proceed as directed in §436.541 of this chapter, except:

(i) A distance of 2.5 ± 0.2 centimeters should be maintained between the lower edge of the stirring blade and the lowest inner surface of the vessel during test rather than 4.5 ± 0.5 centimeters as specified in paragraph (a) of that section; and

(ii) In lieu of paragraph (d) of that section, use the interpretation described in the United States Pharmacopoeia XX dissolution test.


§ 442.154 Cefpodoxime proxetil oral dosage forms.

§ 442.154a Cefpodoxime proxetil tablets.

(a) Requirements for certification—(1)

Standards of identity, strength, quality, and purity. Cefpodoxime proxetil tablets are composed of cefpodoxime proxetil and one or more suitable and harmless diluents, binders, lubricants, colorings, and coating substances. Each tablet contains cefpodoxime proxetil equivalent to either 100 milligrams or 200 milligrams of cefpodoxime. Its cefpodoxime proxetil content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of cefpodoxime that it is represented to contain. Its loss on drying is not more than 5 percent. It passes the dissolution test. It passes the identity test. The cefpodoxime proxetil used conforms to the standards prescribed by §442.54(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The cefpodoxime proxetil used in making the batch for potency, isomer ratio, moisture, and identity.

(B) The batch for content, loss on drying, dissolution, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The cefpodoxime proxetil used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch: A minimum of 100 tablets.

(b) Tests and methods of assay—(1)

Cefpodoxime content. Proceed as directed in §442.54(b)(1), preparing the sample solution and calculating the cefpodoxime content as follows:

(i) Preparation of sample solution. Obtain the average tablet weight of at least 20 tablets. Grind the tablets using a mortar and pestle. Weigh approximately 660 milligrams into a suitable container. Add 30 milliliters of internal standard solution. Shake for 30 minutes using a horizontal platform shaker or equivalent. Centrifuge for about 10 minutes at 3,000 revolutions per minute until the particulate matter has settled. Withdraw a 1 milliliter aliquot of the supernatant and dilute with 9 milliliters of dilution solvent. The sample solutions are stable for at least 48 hours. Refrigeration is not recommended.
(ii) Calculations. Calculate the cefpodoxime content as follows:

\[
\text{Milligrams of cefpodoxime per tablet} = \left( \frac{R_{\text{sam}}}{R_{\text{std}}} \right) \times \left( \frac{W_{\text{sam}}}{W_{\text{std}}} \right) \times (F_1 / F_2) \times F_3 \times F_4 \times P
\]

where:
- \(R_{\text{sam}}\) = Ratio of cefpodoxime proxetil peaks area (sum of both epimers) to the internal standard peak area in the sample preparation;
- \(R_{\text{std}}\) = Ratio of cefpodoxime proxetil peaks area (sum of both epimers) to the internal standard peak area in the standard preparation;
- \(W_{\text{sam}}\) = Weight of cefpodoxime proxetil reference standard, in milligrams;
- \(W_{\text{std}}\) = Weight of sample, in milligrams;
- \(F_1\) = Volume of internal standard used in the sample preparation, in milliliters;
- \(F_2\) = Volume of internal standard used in the standard preparation, in milliliters;
- \(F_3\) = Volume of internal standard used in the standard preparation, in milliliters;
- \(F_4\) = Average tablet weight, i.e., weight of tablets used in sample preparation divided by the number of tablets; and
- \(P\) = Purity of the cefpodoxime proxetil reference standard, expressed as a decimal.

(2) Loss on drying. Proceed as directed in §436.200(a) of this chapter, except dry the sample at a temperature of 80°C and a pressure of 5 millimeters of mercury or less for 16 hours.

(3) Dissolution test. Proceed as directed in §436.215 of this chapter. The quantity Q (the amount of cefpodoxime activity dissolved) is 70 percent within 30 minutes.

(4) Identity. Using the high-performance liquid chromatographic procedure described in paragraph (b)(1) of this section, the retention times for the peaks of the active ingredients must be within 2 percent of the retention times for the peaks of the corresponding reference standards.

[60 FR 58232, Nov. 27, 1995]

§442.154b Cefpodoxime proxetil granules for oral suspension.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefpodoxime proxetil granules for oral suspension is cefpodoxime proxetil and one or more suitable and harmless preservatives, sweeteners, suspending agents, buffers, and flavorings. When constituted as directed in the labeling, each milliliter contains the equivalent of either 10 or 20 milligrams cefpodoxime activity. Its cefpodoxime proxetil content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of cefpodoxime that it is represented to contain. Its loss on drying is not more than 0.5 percent. When constituted as described in the labeling, the pH of the suspension is not less than 4 and not more than 5.5. It passes the identity test. The cefpodoxime proxetil used conforms to the standards prescribed by §442.54(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:
- (A) The cefpodoxime proxetil used in making the batch for potency, isomer ratio, moisture, and identity.
- (B) The batch for content, loss on drying, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:
- (A) The cefpodoxime proxetil used in making the batch: 10 packages, each containing approximately 500 milligrams.
- (B) The batch: A minimum of 10 intermediate containers.

(b) Tests and methods of assay—(1) Cefpodoxime content. Proceed as directed in §442.54(b)(1), preparing the sample solution and calculating the cefpodoxime content as follows:

(i) Preparation of sample solution. Reconstitute as directed in the labeling. Immediately before sampling the suspension, shake vigorously for several
seconds. Into a suitable container, accurately weigh out 6 grams of the 50 milligrams per 5 milliliters suspension, or 3 grams of the 100 milligrams per 5 milliliters suspension. Add 5 milliliters of internal standard solution and 25 milliliters of dilution solvent. Shake for 30 minutes using a horizontal platform shaker or equivalent. Centrifuge for about 10 minutes at 3,000 revolutions per minute until the particulate matter has settled. Withdraw a 1 milliliter aliquot of the supernatant and dilute with 1 milliliter of dilution solvent. The sample solutions are stable for at least 48 hours. Refrigeration is not recommended.

(ii) Calculations. Calculate the cefpodoxime content as follows:

\[
\text{Milligrams of cefpodoxime per 5 milliliters of suspension} = \left( \frac{R_{\text{sam}}}{R_{\text{std}}} \right) \times \left( \frac{W_{\text{std}}}{W_{\text{sam}}} \right) \times \left( \frac{F_{1}}{F_{4}} \right) \times \left( \frac{F_{2}}{F_{4}} \right) \times F_{5} \times P
\]

where:
- \(R_{\text{sam}}\) = Ratio of cefpodoxime proxetil peaks area (sum of both epimers) to the internal standard peak area in the sample preparation;
- \(R_{\text{std}}\) = Ratio of cefpodoxime proxetil peaks area (sum of both epimers) to the internal standard peak area in the standard preparation;
- \(W_{\text{sam}}\) = Weight of cefpodoxime proxetil reference standard, in milligrams;
- \(W_{\text{std}}\) = Weight of sample, in grams;
- \(F_{1}\) = Volume of internal standard used in the sample preparation, in milliliters;
- \(F_{2}\) = 0.766; The ratio of molecular weight for free-acid cefpodoxime over the molecular weight of cefpodoxime proxetil (427.46/557.61);
- \(F_{4}\) = 0.2; Factor to convert to 5 milliliters;
- \(F_{5}\) = Specific gravity of suspension for milligram per 5 milliliters calculated on the air-free basis (specific gravity is determined on a sample of suspension that has been shaken gently on a platform shaker under vacuum for 2 hours); and
- \(P\) = Purity of the cefpodoxime proxetil reference standard, expressed as a decimal.

(2) Loss on drying. Proceed as directed in §436.200(a) of this chapter, except dry the sample at a temperature of 80°C and a pressure of 5 millimeters of mercury or less for 16 hours.

(3) pH. Proceed as directed in §436.202 of this chapter, using the drug constituted as directed in the labeling.

(4) Identity. Using the high-performance liquid chromatographic procedure described in paragraph (b)(1) of this section, the retention times for the peaks of the active ingredients must be within 2 percent of the retention times for the peaks of the corresponding reference standards.

§ 442.180 Cefprozil oral dosage forms.

§ 442.180a Cefprozil tablets.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefprozil tablets are composed of cefprozil and one or more suitable and harmless diluents, binders, lubricants, colorings, and coating substances. Each tablet contains cefprozil equivalent to either 250 milligrams or 500 milligrams of anhydrous cefprozil. The cefprozil content of the tablets is satisfactory if it is not less than 90 percent nor more than 120 percent of the number of milligrams of anhydrous cefprozil that it is represented to contain. The moisture content of the tablets is not more than 7 percent. The tablets pass the dissolution test. The tablets pass the identity tests. The cefprozil used conforms to the standards prescribed by §442.80(a)(1) of this part.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The cefprozil used in making the batch for potency, E-isomer ratio, moisture, pH, crystallinity, and identity.

(B) The batch for content, moisture, dissolution, and identity.
(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:
(A) The cefprozil used in making the batch: 10 packages, each containing approximately 500 milligrams.
(B) The batch: A minimum of 100 tablets.
(b) Tests and methods of assay—(1) Cefprozil content. Proceed as directed in §442.80(b)(1) of this part, preparing the sample solution and calculating the cefprozil content as follows:
(i) Preparation of sample solution. Place one or a known number of intact tablets into a 250-milliliter volumetric flask containing about 180 milliliters of distilled water. Allow the tablet(s) to disintegrate as aided by swirling and brief ultrasonication. Dilute the contents to volume with distilled water and mix thoroughly. Transfer an aliquot of this solution to a volumetric flask of suitable size to obtain a solution containing 0.3 milligram per milliliter of cefprozil (estimated) when diluted to volume with water. Filter through a 0.45 micron filter prior to injection into the chromatographic system.
(ii) Calculations. Calculate the cefprozil content as follows:

\[
\text{Milligrams of cefprozil per tablet} = \frac{A_U}{A_S} \times P \times d \times \frac{n}{1,000}
\]

where:
- \(A_U\) = Area of the cefprozil (Z) or cefprozil (E) response in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_S\) = Area of the cefprozil (Z) or cefprozil (E) response in the chromatogram of the cefprozil (Z) or the cefprozil (E) working standard;
- \(P\) = Cefprozil (Z) or cefprozil (E) activity in the cefprozil (Z) or the cefprozil (E) working standard solution in micrograms per milliliter;
- \(d\) = Dilution factor of the sample; and
- \(n\) = Number of tablets taken in the sample.

(2) Moisture. Proceed as directed in §436.201 of this chapter.
(3) Dissolution test. Proceed as directed in §436.215 of this chapter. The quantity Q (the amount of cefprozil activity dissolved) is 75 percent at 45 minutes.
(4) Identity—(i) High performance liquid chromatography. Using the high performance liquid chromatographic procedure described in paragraph (b)(1) of this section, the retention times for the responses of the active ingredients must be within 2 percent of the retention times for the responses of the corresponding reference standards.
(ii) Thin layer chromatography. Proceed as directed in §436.368 of this chapter.
§442.180b Cefprozil for oral suspension.
(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefprozil for oral suspension is cefprozil with one or more suitable and harmless preservatives, sweeteners, suspending agents, buffers, and flavorings. The cefprozil content of the oral suspension is satisfactory if it is not less than 90 percent nor more than 120 percent of the number of milligrams of anhydrous cefprozil that it is represented to contain. When constituted as directed in the labeling, each milliliter contains the equivalent of either 25 or 50 milligrams anhydrous cefprozil activity. Its moisture content is not more than 3 percent. When constituted as described in the labeling, the pH of the suspension is not less than 4.0 nor more than 6.0. It passes the identity tests. The cefprozil used conforms to the standards prescribed by §442.80(a)(1) of this part.
(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.
(3) Requests for certification samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:
(i) Results of tests and assays on:
(A) The cefprozil used in making the batch for potency, E-isomer ratio, moisture, \(\text{pH}\), crystallinity, and identity.
(B) The batch for content, moisture, \(\text{pH}\), and identity.
(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:
(A) The cefprozil used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch: A minimum of 10 intermediate containers.

(b) Tests and methods of assay—

(1) Cefprozil content. Proceed as directed in §442.80(b)(1), preparing the sample solution and calculating the cefprozil content as follows:

(i) Preparation of sample solution. Constitute as directed in the labeling. Transfer a portion of the suspension containing 250 milligrams (estimated) of cefprozil into a 250-milliliter volumetric flask using a glass syringe and a 13-gauge needle. Dilute to volume with water, ultrasonicate briefly to dissolve and mix well. Transfer a 15-milliliter aliquot of this solution to a 50-milliliter volumetric flask and dilute to volume with water to obtain a solution containing 0.3 milligram per milliliter of cefprozil (estimated). Filter through a 0.45 micron filter prior to injection into the chromatographic system.

(ii) Calculations. Calculate the cefprozil content as follows:

\[
\text{Milligrams of cefprozil (Z) or cefprozil (E) per 5 mL of sample} = \frac{A_u \times P \times d \times 5}{A_s \times 1,000 \times V} + \frac{A_u \times P \times d \times 5}{A_s \times 1,000 \times V}
\]

where:

- \(A_u\) = Area of the cefprozil (Z) or cefprozil (E) response in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the cefprozil (Z) or cefprozil (E) response in the chromatogram of the cefprozil (Z) or the cefprozil (E) working standard;
- \(P\) = Cefprozil (Z) or cefprozil (E) activity in the cefprozil (Z) or the cefprozil (E) working standard solution in micrograms per milliliter;
- \(d\) = Dilution factor of the sample; and
- \(V\) = Volume of sample taken in milliliters.

(2) Moisture. Proceed as directed in §436.202 of this chapter.

(3) pH. Proceed as directed in §436.202 of this chapter, using the drug constituted as directed in the labeling.

(4) Identity—

(i) High performance liquid chromatography. Using the high-performance liquid chromatographic procedure described in paragraph (b)(1) of this section, the retention times for the responses of the active ingredients must be within 2 percent of the retention times for the responses of the corresponding reference standards.

(ii) Thin layer chromatography. Proceed as directed in §436.368 of this chapter.

[58 FR 26661, May 4, 1993]

Subpart C—Injectable Dosage Forms

§ 442.208 Cefamandole nafate for injection.

(a) Requirements for certification—

(1) Standards of identity, strength, quality, and purity. Cefamandole nafate for injection is a dry mixture of cefamandole nafate and one or more suitable and harmless buffering agents. The cefamandole nafate may be isolated in the manufacture of cefamandole nafate for injection. Its cefamandole content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cefamandole that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 3.0 percent. Its pH is not less than 6.0 and not more than 8.0. If isolated, the cefamandole nafate used conforms to the standards prescribed by §442.8a(a)(1). If the cefamandole nafate is not isolated, the potency of the dry mixture is not less than 810 micrograms and not more than 1,000 micrograms of cefamandole per milligram on an anhydrous basis when corrected for sodium carbonate; and the dry mixture gives a positive identity test.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) If isolated, the cefamandole nafate used in making the batch for

(b) Cefamandole content, moisture, pH, and identity.

(4) Identity—

(i) High performance liquid chromatography. Using the high-per-
Food and Drug Administration, HHS § 442.208

(b) The batch for cefamandole content, sterility, pyrogens, moisture, and pH. In addition, if the cefamandole nafate is not isolated, results of tests and assays on the dry mixture for potency and identity.

(ii) Samples required:
(a) For all tests except sterility: A minimum of 10 immediate containers, unless the cefamandole nafate is not isolated, a minimum of 15 immediate containers.
(b) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Cefamandole content. Proceed as directed in §436.324 of this chapter, preparing the sample solution and calculating the cefamandole content as follows:
(i) Sample preparation. Reconstitute the sample as directed in the labeling. If it is represented as a single dose container, remove all of the withdrawable contents with a suitable hypodermic needle and syringe. If the labeling specifies the amount of cefamandole content in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Further dilute an aliquot of this solution with distilled water to obtain a concentration of 2.0 milligrams of cefamandole per milliliter (estimated). Transfer 5 milliliters of this solution to a 50-milliliter volumetric flask, add 30 milliliters of pH 2.3 buffer, dilute to volume with distilled water, and mix. In addition, if the cefamandole nafate is not isolated, prepare the sample solution as described in §436.324(d) of this chapter. Determine the sodium carbonate content as follows: Dissolve an accurately weighed portion of the dry mixture, approximately 1.0 gram, with approximately 100 milliliters of distilled water. Titrate with 0.2N hydrochloric acid. Determine the end-point potentiometrically to the first equivalent using a glass calomel combination electrode. Each milliliter of 0.2N hydrochloric acid is equivalent to 21.2 milligrams of sodium carbonate.
(ii) Calculations—(a) Calculate the cefamandole content as follows:

\[
\text{Milligrams of cefamandole} = \frac{A \times \text{Milligrams of working standard} \times f}{B \times 50 \times 1,000}
\]

where:
- \(A\) = The peak height of the sample;
- \(B\) = The peak height of the working standard; and
- \(f\) = The dilution factor of the sample.

(b) If the cefamandole nafate is not isolated in the manufacture of cefamandole nafate for injection, calculate the micrograms of cefamandole per milligram of sample as described in §436.324(f) of this chapter. The micrograms per milligram of cefamandole is corrected for sodium carbonate content and moisture content.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cefamandole per milliliter.

(4) [Reserved]

(5) Moisture. Proceed as directed in §436.201 of this chapter.

(6) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter, except determine the pH 30 minutes after preparation of the sample solution.
§ 442.209 Cefamandole sodium for injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefamandole sodium for injection is a dry mixture of cefamandole sodium and one or more suitable and harmless buffering agents. Its cefamandole content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cefamandole that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 3.0 percent. Its pH is not less than 6.0 and not more than 8.5. The cefamandole sodium used conforms to the standards prescribed by §442.9a(a)(1).

(b) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cefamandole sodium used in making the batch for cefamandole content, moisture, pH, and identity.

(b) The batch for cefamandole content, sterility, pyrogens, moisture, and pH.

(ii) Samples required:

(a) The cefamandole sodium used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Cefamandole content. Proceed as directed in §436.324 of this chapter, preparing the sample solution and calculating the cefamandole content as follows:

(i) Sample solution. Reconstitute the sample as directed in the labeling. If it is represented as a single-dose container, remove all the withdrawable contents with a suitable hypodermic needle and syringe. If the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Further dilute an aliquot of this solution with distilled water to obtain a concentration of 2.0 milligrams of cefamandole per milliliter (estimated). Transfer 5 milliliters of this solution to a 50-milliliter volumetric flask, add 30 milliliters of pH 2.3 buffer, dilute to volume with distilled water, and mix.

(ii) Calculations. Calculate the cefamandole content as follows:

\[
\text{Potency of working standard per milligram} = \frac{A \times \text{Milligrams of working standard}}{B \times 50 \times 1,000} \times f
\]

where:

\[A = \text{The peak height of the sample;}\]

\[B = \text{The peak height of the working standard;}\]

\[f = \text{The dilution factor of the sample.}\]

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cefamandole per milliliter.

(4) [Reserved]
§ 442.211 Cefazolin sodium injectable dosage forms.

§ 442.211a Sterile cefazolin sodium.

The requirements for certification and the tests and methods of assay for sterile cefazolin sodium packaged for dispensing are described in § 442.11a, except for the following additional requirements if it is packaged with lidocaine hydrochloride injection 0.5 percent U.S.P.:

(a) The pH, when reconstituted and diluted to 100 milligrams per milliliter with lidocaine hydrochloride injection 0.5 percent U.S.P., is not less than 5.5 and not more than 7.0.

(b) In addition to the information required by § 442.11a (a)(3)(i), the following shall be submitted:

(1) The pH on the batch reconstituted with lidocaine hydrochloride injection 0.5 percent U.S.P.;

(2) Results of tests and assays on the lidocaine hydrochloride injection 0.5 percent to show conformance with U.S.P. requirements.

§ 442.211b Cefazolin sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefazolin sodium injection is a frozen aqueous solution of cefazolin sodium in an isoosmotic diluent. Each milliliter contains cefazolin sodium equivalent to either 10 milligrams or 20 milligrams of cefazolin per milliliter. Its cefazolin content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cefazolin that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 4.5 and not more than 7.0. It passes the identity test. The cefazolin used conforms to the standards prescribed by § 442.10(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Requests of tests and assays on:

(a) The cefazolin used in making the batch for cefazolin content, moisture, heavy metals, and identity.

(b) The batch for cefazolin content, sterility, pyrogens, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) The cefazolin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Cefazolin content. Proceed as directed in § 436.342 of this chapter, preparing the sample solution and calculating the cefazolin content as follows:

(i) Preparation of sample solution. Using a suitable hypodermic needle and syringe, transfer an accurately measured representative portion from each container, equivalent to 40 milligrams of cefazolin, to a 100-milliliter volumetric flask. Dilute to volume with buffer solution, pH 7.0, and mix. Transfer 10.0 milliliters of this solution to a 200-milliliter volumetric flask, add 5.0 milliliters of internal standard solution, dilute to volume with buffer solution, pH 7.0, and mix.

(ii) Calculation. Calculate the milligrams of cefazolin per milliliter of sample as follows:

\[
\text{Milligrams of cefazolin per milliliter = } \frac{R_u \times P_s \times d}{R_s \times 1,000}
\]

where:

- \( R_u \) = Area of the cefazolin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \( P_s \) = Area of internal standard peak;
- \( R_s \) = Area of cefazolin peak in the chromatogram of the cefazolin working standard;
- \( d \) = Area of internal standard peak.
§ 442.212 Cefoperazone injectable dosage forms.

§ 442.212a Sterile cefoperazone sodium.

The requirements for certification and the tests and methods of assay for sterile cefoperazone sodium packaged for dispensing are described in §442.12a.


§ 442.212b Cefoperazone sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefoperazone sodium injection is a frozen aqueous iso-osmotic solution of cefoperazone sodium which may contain one or more suitable and harmless buffer substances in a diluent. Each milliliter contains cefoperazone sodium equivalent to either 20 milligrams or 40 milligrams of cefoperazone per milliliter. Its cefoperazone content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefoperazone that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 4.5 and not more than 6.5. It passes the identity test. The cefoperazone sodium used conforms to the standards prescribed by §442.12(a)(1).

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(a) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 50 milligrams of cefoperazone per kilogram.

(4) pH. Proceed as directed in §436.202 of this chapter, using the undiluted solution.

(5) Identity. The high-pressure liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cefazolin working standard.

§ 442.212 Cefazolin activity in the cefazolin working standard solution in micrograms per milliliter; and

d=Dilution factor of the sample.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(a) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 50 milligrams of cefazolin per kilogram.

(4) pH. Proceed as directed in §436.202 of this chapter, using the undiluted solution.

(5) Identity. The high-pressure liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cefazolin working standard.

§ 442.212a Sterile cefoperazone sodium.

The requirements for certification and the tests and methods of assay for sterile cefoperazone sodium packaged for dispensing are described in §442.12a.


§ 442.212b Cefoperazone sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefoperazone sodium injection is a frozen aqueous iso-osmotic solution of cefoperazone sodium which may contain one or more suitable and harmless buffer substances in a diluent. Each milliliter contains cefoperazone sodium equivalent to either 20 milligrams or 40 milligrams of cefoperazone per milliliter. Its cefoperazone content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefoperazone that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 4.5 and not more than 6.5. It passes the identity test. The cefoperazone sodium used conforms to the standards prescribed by §442.12(a)(1).

(2) Sterility. Proceed as directed in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cefoperazone sodium used in making the batch for potency, moisture, pH, and identity.

(b) The batch for potency, sterility, pyrogens, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) The cefoperazone sodium used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay. Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) Potency. Proceed as directed in §436.338 of this chapter, preparing the sample solution and calculating the cefoperazone content as follows:

(i) Sample solution. Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with mobile phase to obtain a solution containing 160 micrograms per milliliter (estimated).

(ii) Calculations. Calculate the milligrams of cefoperazone per milliliter of sample as follows:

\[
\text{Milligrams of cefoperazone per milliliter} = \frac{A_u \times P \times d}{A_s \times 1,000}
\]

where:

\(A_u\) = Area of the cefoperazone peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

\(A_s\) = Area of the cefoperazone peak in the chromatogram of the cefoperazone working standard;
§ 442.213b Cefotaxime sodium injectable dosage forms.

§ 442.213a Sterile cefotaxime sodium.

The requirements for certification and the tests and methods of assay for sterile cefotaxime sodium packaged for dispensing are described in §442.13a.


§ 442.213b Cefotaxime sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefotaxime sodium injection is a frozen aqueous solution of cefotaxime sodium with one or more suitable and harmless buffer substances in an isosmotic diluent. Each milliliter contains cefotaxime sodium equivalent to either 20 milligrams or 40 milligrams of cefotaxime per milliliter. Its cefotaxime content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of cefotaxime that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 5.0 and not more than 7.5. It passes the identity test. The cefotaxime sodium used conforms to the standards prescribed by §442.13(a)(1).

(2) Potency. Proceed as directed in §436.105 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(4) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cefotaxime sodium used in making the batch for potency, moisture, pH, and identity.

(b) The batch for potency, sterility, pyrogens, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) The cefotaxime sodium used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay. Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) Potency. Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 2.0 micrograms of cefotaxime per milliliter (estimated).

(ii) Hydroxylamine colorimetric assay. Proceed as directed in §436.205 of this chapter, preparing the sample as follows: Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with distilled water to give a stock solution of convenient concentration. Further dilute...
with distilled water to the prescribed concentration.

(2) Sterility. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in § 436.32(a) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 50 milligrams of cefotaxime per kilogram.

(4) pH. Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

(5) Identity. Proceed as directed in § 436.323 of this chapter, except prepare spotting solutions as follows: Prepare solutions of the sample and working standard, each containing 1 milligram of cefotaxime per milliliter in distilled water.

§ 442.214 Cefoxitin injectable dosage forms.

§ 442.214a Sterile cefoxitin sodium.

The requirements for certification and the tests and methods of assay for sterile cefoxitin packaged for dispensing are described in § 442.14a.


§ 442.214b Cefoxitin sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefoxitin sodium injection is a frozen aqueous solution of cefoxitin sodium with one or more suitable and harmless buffer substances in an isotonic diluent. Each milliliter contains cefoxitin sodium equivalent to either 20 or 40 milligrams of cefoxitin. Its cefoxitin content is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefoxitin that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 4.5 and not more than 8.0. It passes the identity test. The cefoxitin sodium used conforms to the standards prescribed by § 442.14(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cefoxitin sodium used in making the batch for cefoxitin content, moisture, pH, identity, and crystallinity.

(b) The batch for cefoxitin content, sterility, pyrogens, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) The cefoxitin sodium used in making the batch: 10 packages, each containing approximately 50 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay. Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) Cefoxitin content. Proceed as directed in § 436.347 of this chapter, preparing the working standard and sample solutions and calculating the cefoxitin content as follows:

(i) Working standard solution. Dissolve an accurately weighed portion of the cefoxitin working standard with water to obtain a solution containing 200 micrograms of cefoxitin per milliliter.

(ii) Sample solution. Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with sufficient water to obtain a solution containing 200 micrograms of cefoxitin per milliliter (estimated).

(iii) Calculations. Calculate the milligrams of cefoxitin per milliliter of sample as follows:
Milligrams of cefoxitin per milliliter = \frac{A_u \times P_s \times d}{A_s \times 1,000}

where:
- \(A_u\) = Area of the cefoxitin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the cefoxitin peak in the chromatogram of the cefoxitin working standard;
- \(P_s\) = Cefoxitin activity in the cefoxitin working standard solution in micrograms per milliliter; and
- \(d\) = Dilution factor of the sample.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(a) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 50 milligrams of cefoxitin per kilogram.

(4) pH. Proceed as directed in §436.202 of this chapter, using the undiluted solution.

(5) Identity. The high-pressure liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cefoxitin working standard.

§ 442.216a

per milligram of sample and milligrams of ceftazidime per container. Proceed as directed in §442.16a(b)(1), preparing the sample solutions and calculating the potency and content as follows:

(i) Preparation of sample solutions. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(i) (a) and (b) of this section.

(a) Ceftazidime potency (micrograms of ceftazidime per milligram). Accurately weigh and dissolve approximately 350 milligrams of ceftazidime sample in distilled water and dilute to volume in a 250-milliliter volumetric flask to obtain a stock solution containing approximately 1,000 micrograms of ceftazidime per milliliter. Mix well. Immediately prior to chromatography, further dilute 5 milliliters of stock solution to 50 milliliters with water to obtain a solution containing 100 micrograms of ceftazidime activity per milliliter (estimated).

(b) Ceftazidime content (milligrams of ceftazidime per vial). Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Further dilute an aliquot of this solution with distilled water to obtain a concentration of 1.0 milligram per milliliter (estimated). Immediately prior to chromatography, dilute 5.0 milliliters of the sample solution to 50 milliliters with water.

(ii) Calculations—(a) Ceftazidime potency (micrograms per milligram). Calculate the micrograms of ceftazidime per milligram as follows:

Micrograms of ceftazidime = \( \frac{A_s \times P_s \times 100}{A_r \times C_u \times (100 - m - S - A)} \)

where:
- \( A_r \) = Area of the ceftazidime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \( P_s \) = Ceftazidime activity in the ceftazidime working standard solution in micrograms per milliliter;
- \( C_u \) = Milligrams of sample per milliliter of sample solution;
- \( m \) = Percent loss on drying (determined as directed in §436.200(h) of this chapter if the formulation contains sodium carbonate and determined as directed in §436.200(g) of this chapter if the formulation contains L-arginine);
- \( S \) = Percent sodium carbonate content of the sample (determined as directed in §436.357 of this chapter); and
- \( A \) = Percent L-arginine content of the sample (determined as directed in §455.204 of this chapter, except use ceftazidime instead of aztreonam in the working standard solution and use water instead of mobile phase). Prepare the sample solution by diluting an accurately weighed portion of the contents of a vial with water to 0.2 milligram per milliliter (estimated). The resolution between the ceftazidime peak and the arginine peak is not less than 6.0, the asymmetry factor for the arginine peak is not more than 4.0.

(b) Ceftazidime content (milligrams of ceftazidime per vial). Calculate the ceftazidime content of the vial as follows:

\[
\text{Milligrams of ceftazidime per vial} = \frac{A_s \times P_s \times d}{A_r \times 1,000}
\]

where:
- \( A_s \) = Area of the ceftazidime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \( A_r \) = Area of the ceftazidime peak in the chromatogram of the ceftazidime working standard; and
- \( d \) = Dilution factor of the sample.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 80 milligrams of ceftazidime per milliliter.

(4) Loss on drying. Proceed as directed in §436.200(h) of this chapter if the formulation contains sodium carbonate and as directed in §436.200(g) of this chapter if the formulation contains L-arginine.
(5) pH. Proceed as directed in § 436.202 of this chapter, preparing the sample solution as follows: reconstitute the sample in the sealed container to give an aqueous solution containing approximately 100 milligrams per milliliter, relieving the pressure inside the container if necessary during the reconstitution.

(6) Pyridine content. Proceed as directed in § 436.358 of this chapter, using a temperature of 40 °C, an ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (5 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silicas, a flow rate of 1.6 milliliters per minute, and a known injection volume from 10 to 20 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) Reagents—(a) Phosphate buffer, pH 7.0. Dissolve 5.68 grams of sodium phosphate, dibasic, anhydrous and 3.63 grams of potassium phosphate, monobasic, in water and dilute to 1,000 milliliters.

(b) Mobile phase. Mix 300 milliliters of acetonitrile and 100 milliliters of 0.25M ammonium phosphate, monobasic, dilute to 1,000 milliliters with water and add sufficient 10M ammonia solution to give a pH of 7.0±0.1. Filter the mobile phase through a suitable glass fiber filter or equivalent that is capable of removing particulate contamination to 1 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph pumping system.

(c) System suitability test solution. Prepare a solution in phosphate buffer, pH 7.0, containing 25 micrograms of pyridine and 25 micrograms of an authentic sample of (6R, 7R)-7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(2-t-butoxy-carbonylprop-2-yloxyimino)acetamido]-3-(1-pyridiniummethyl)ceph-3-em-4-carboxylate (t-butyl ceftazidime) per milliliter. Note, if no t-butyl ceftazidime is present in the sample solution, the working standard solution may be substituted for the system suitability test solution and the system suitability requirement for resolution for t-butyl ceftazidime is omitted.

(ii) Preparation of working standard and sample solutions—(a) Working standard solution. Accurately weigh approximately 250 milligrams of pyridine into a 100-milliliter volumetric flask and dilute to volume with water to obtain a stock solution containing approximately 2,500 micrograms of pyridine per milliliter. Mix well. Immediately prior to chromatography, further dilute 2.0 milliliters of stock solution to 200 milliliters with phosphate buffer, pH 7.0, to obtain a solution containing 25 micrograms of pyridine per milliliter.

(b) Sample solution. Accurately weigh approximately 660 milligrams of the sample into a 100-milliliter volumetric flask and add 50 milliliters of phosphate buffer, pH 7.0. Shake until dissolved and dilute to volume with phosphate buffer, pH 7.0. Mix well. Store the solution at a temperature below 15 °C and inject into the chromatograph within 1 hour of preparation.

(iii) System suitability requirements—(a) Tailing factor. The tailing factor (T) is satisfactory if it is not more than 2.5 at 5 percent of peak height.

(b) Resolution. The resolution (R) between the peak for pyridine and the peak for t-butyl ceftazidime is satisfactory if it is not less than 3.

(c) Coefficient of variation. The coefficient of variation (Sx in percent) of five replicate injections is satisfactory if it is not more than 3 percent.

If the system suitability requirements have been met, then proceed as described in § 436.358(b) of this chapter. Alternate chromatographic conditions are acceptable provided reproducibility and resolution are comparable to the system. However, the sample preparation described in paragraph (b)(6)(ii)(b) of this section should not be changed.

(iv) Calculations. Calculate the pyridine content in percent of the sample as follows:

\[
\text{Pyridine content in percent} = \frac{H_u \times P_u \times 0.1}{H_i \times C_u}
\]

where:
§ 442.216b Ceftazidime sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Ceftazidime sodium injection is a frozen, aqueous, iso-osmotic solution of ceftazidime sodium which may contain one or more suitable and harmless buffer substances and a tonicity adjusting agent. Each milliliter contains ceftazidime sodium equivalent to 10, 20, or 40 milligrams of ceftazidime per milliliter. Its ceftazidime content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of ceftazidime that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 5.0 and not more than 7.5 It passes the identity test. The ceftazidime pentahydrate conforms to the standards prescribed by § 442.16(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The ceftazidime pentahydrate used in making the batch: 10 packages, each containing 500 milligrams.

(B) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay. Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) Ceftazidime content. Proceed as directed in § 442.216(b)(3), except prepare the sample solution and calculate the ceftazidime content as follows:

(i) Preparation of sample solution. Remove an accurately measured representative portion from each container immediately after thawing and reaching room temperature and dilute with mobile phase to obtain a solution containing 100 micrograms of ceftazidime per milliliter (estimated). Prepare the sample solution just prior to its introduction into the chromatograph.

(ii) Calculation. Calculate the milligrams of ceftazidime per milliliter of sample as follows:

\[ \text{Milligrams of ceftazidime per milliliter} = \frac{A_u \times P_s \times d}{A_s \times 1,000} \]

where:

- \(A_u\) = Area of the ceftazidime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the ceftazidime peak in the chromatogram of the ceftazidime working standard;
- \(P_s\) = Ceftazidime activity in the ceftazidime working standard solution in micrograms per milliliter; and
- \(d\) = Dilution factor of the sample.

(2) Sterility. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in § 436.32(b) of this chapter, except inject a sufficient volume of the diluted solution to deliver 80 milligrams of ceftazidime per kilogram.

(4) pH. Proceed as directed in § 436.202 of this chapter, using the undiluted solution.
(5) Identify. The high performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the ceftazidime working standard.

[54 FR 40652, Oct. 3, 1989]

§ 442.217 Ceftizoxime injectable dosage forms.

§ 442.217a Sterile ceftizoxime sodium.

The requirements for certification and the tests and methods of assay for sterile ceftizoxime sodium packaged for dispensing are described in § 442.17a.


§ 442.217b Ceftizoxime sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Ceftizoxime sodium injection is a frozen aqueous solution of ceftizoxime sodium with one or more suitable and harmless buffer substances in an isoosmotic diluent. Each milliliter contains ceftizoxime sodium equivalent to either 20 milligrams or 40 milligrams of ceftizoxime per milliliter. Ceftizoxime content is satisfactory if it is not less than 90 percent and not more than 115 percent of the represented number of milligrams of ceftizoxime. It is sterile. It is nonpyrogenic. Its pH is not less than 5.5 and not more than 8.0. It passes the identity test. The ceftizoxime sodium used conforms to the standards prescribed by § 442.17(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The ceftizoxime sodium used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assays. Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) Ceftizoxime content. Proceed as directed in § 436.345 of this chapter, except prepare the sample solution and calculate the ceftizoxime content as follows:

(i) Sample solution. Using a suitable hypodermic needle and syringe, transfer an accurately measured representative portion from each container, equivalent to 40 milligrams of ceftizoxime, to a 100-milliliter volumetric flask. Dilute to volume with pH 7.0 buffer solution and mix. Transfer 10.0 milliliters of this solution to a 200-milliliter volumetric flask, add 5.0 milliliters of internal standard solution, dilute to volume with pH 7.0 buffer solution, and mix.

(ii) Calculations. Calculate the milligrams of ceftizoxime per milliliter of sample as follows:

\[
\text{Milligrams of ceftizoxime per milliliter} = \frac{R_c \times P_s \times d}{R_u \times 1,000},
\]

where:

- \( R_c \) = Area of the ceftizoxime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard)/Area of the internal standard peak;
- \( R_u \) = Area of the ceftizoxime peak in the chromatogram of the ceftizoxime working standard/Area of the internal standard peak;
- \( P_s \) = Ceftizoxime activity in the ceftizoxime working standard solution in micrograms per milliliter; and
- \( d \) = Dilution factor of the sample.

(2) Sterility. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in § 436.32(a) of this chapter, except inject...
§ 442.218 Cefuroxime injectable dosage forms.

§ 442.218a Sterile cefuroxime sodium.

The requirements for certification and the tests and methods of assay for sterile cefuroxime sodium packaged for dispensing are described in § 442.18a.

§ 442.218b Cefuroxime sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefuroxime sodium injection is a frozen, aqueous, iso-osmotic solution of cefuroxime sodium which may contain one or more suitable and harmless buffer substances and a tonicity adjusting agent. Each milliliter contains cefuroxime sodium equivalent to 15 or 30 milligrams of cefuroxime per milliliter. Its cefuroxime content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefuroxime that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 5.0 and not more than 7.5. It passes the identity test. The cefuroxime sodium used conforms to the standards prescribed by § 442.18(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 432.5 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The cefuroxime sodium used in making the batch for potency, moisture, pH, and identity.

(B) The batch for cefuroxime content, sterility, pyrogens, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The cefuroxime sodium used in making the batch: 10 packages, each containing 1 gram.

(B) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(3) Tests and methods of assay—Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) Cefuroxime content. Proceed as directed in § 436.343 of this chapter, except prepare the sample solution and calculate the cefuroxime content as follows:

(i) Preparation of sample solution. Remove an accurately measured representative portion from each container immediately after thawing and reaching room temperature and dilute with water to obtain a solution containing 50 micrograms of cefuroxime per milliliter (estimated). Prepare the sample solution just prior to its introduction in the chromatograph.

(ii) Calculation. Calculate the milligrams of cefuroxime per milliliter of sample as follows:

\[ \text{Milligrams of cefuroxime per milliliter} = \frac{A_u \times P_s \times d}{A_s \times 1,000} \]

where:

- \( A_u \): Area of the cefuroxime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \( A_s \): Area of the cefuroxime peak in the chromatogram of the cefuroxime working standard;
- \( P_s \): Cefuroxime activity in the cefuroxime working standard solution in micrograms per milliliter; and
- \( d \): Dilution factor of the sample.

(2) Sterility. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.
§ 442.220 Sterile cefonicid sodium.

The requirements for certification and the tests and methods of assay for sterile cefonicid sodium packaged for dispensing are described in §442.20a.

§ 442.222 Cefmenoxime hydrochloride for injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefmenoxime hydrochloride for injection is a dry mixture of cefmenoxime hydrochloride and sodium carbonate. Each milligram of cefmenoxime hydrochloride for injection contains not less than 869 and not more than 1,015 micrograms of cefmenoxime on an anhydrous and sodium carbonate-free basis. Its cefmenoxime content is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of cefmenoxime that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 1.5 percent. Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 6.4 and not more than 7.9. The cefmenoxime hydrochloride used in making the batch for cefmenoxime content, moisture, identity, and crystallinity.

(b) The batch for cefmenoxime content, sterility, pyrogens, loss on drying, pH, and sodium carbonate content.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The cefmenoxime hydrochloride used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Cefmenoxime content. Proceed as directed in §436.32(b) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 50 milligrams of cefuroxime per kilogram.

(4) pH. Proceed as directed in §436.202 of this chapter, using the undiluted solution.

(5) Identity. The high performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cefuroxime working standard.

[54 FR 40654, Oct. 3, 1989]

§ 442.222 Cefmenoxime hydrochloride for injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefmenoxime hydrochloride for injection is a dry mixture of cefmenoxime hydrochloride and sodium carbonate. Each milligram of cefmenoxime hydrochloride for injection contains not less than 869 and not more than 1,015 micrograms of cefmenoxime on an anhydrous and sodium carbonate-free basis. Its cefmenoxime content is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of cefmenoxime that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 1.5 percent. Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 6.4 and not more than 7.9. The cefmenoxime hydrochloride used in making the batch for cefmenoxime content, moisture, identity, and crystallinity.

(b) The batch for cefmenoxime content, sterility, pyrogens, loss on drying, pH, and sodium carbonate content.

(iii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The cefmenoxime hydrochloride used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Cefmenoxime content. Proceed as directed in §436.363 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silicas, a flow rate not to exceed 2.0 milliliters per minute, and a known injection volume between 10 and 20 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) Reagents—(A) 0.1M Phosphate buffer solution, pH 6.8. Dissolve 6.4 grams of monobasic potassium phosphate and 18.9 grams of dibasic sodium phosphate in 750 milliliters of water. Adjust the pH to 6.8 with 1N sodium hydroxide and dilute to 1,000 milliliters.

(B) Internal standard solution. Dissolve and dilute 0.15 gram of phthalimide in methanol to 100 milliliters.

(C) Mobile phase. Mix water:acetonitrile:glacial acetic acid (50:10:1). Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) Preparation of working standard and sample solutions—(A) Working standard solution. Dissolve approximately 50 milligrams of the cefmenoxime working standard, accurately weighed, in 10
milliliters of 0.1M phosphate buffer solution, pH 6.8 and dilute to 50 milliliters with mobile phase. Transfer 4.0 milliliters of this solution to a 50-milliliter volumetric flask, add 20 milliliters of internal standard solution and dilute to volume with mobile phase to obtain a solution containing 80 micrograms of cefmenoxime per milliliter.

(B) Sample solutions. Determine both micrograms of cefmenoxime per milligram of the sample and micrograms of cefmenoxime per container. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(ii)(B) (1) and (2) of this section.

(1) Micrograms of cefmenoxime per milligram. Dissolve the accurately weighed dry contents of a sample with sufficient distilled water to obtain a solution containing 1 milligram of cefmenoxime per milliliter (estimated). Transfer 4.0 milliliters of this solution to a 50-milliliter volumetric flask, add 20 milliliters of internal standard solution and dilute to volume with mobile phase to obtain a solution containing 80 micrograms of cefmenoxime per milliliter (estimated).

(2) Milligrams of cefmenoxime per container. Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute the solution thus obtained with sufficient distilled water to obtain a solution containing 1 milligram of cefmenoxime per milliliter (estimated). Transfer 4.0 milliliters of this solution to a 50-milliliter volumetric flask, add 20 milliliters of internal standard solution and dilute to volume with mobile phase to obtain a solution containing 80 micrograms of cefmenoxime per milliliter (estimated).

(iii) System suitability requirements—
(A) Tailing factor. The tailing factor (T) for the cefmenoxime peak is satisfactory if it is not more than 1.6 at 5 percent of peak height.

(B) Efficiency of the column. The efficiency of the column (n) is satisfactory if it is greater than 1,200 theoretical plates for the cefmenoxime peak.

(C) Resolution. The resolution (R) between the peak for cefmenoxime and phthalimide is satisfactory if it is not less than 2.3.

(D) Coefficient of variation. The coefficient of variation (S\textsubscript{v}) in percent of 5 replicate injections is satisfactory if it is not more than 2.0 percent. If the system suitability requirements have been met, then proceed as described in §436.363(b) of this chapter.

(iv) Calculations—(A) Micrograms per milligram. Calculate the micrograms of cefmenoxime per milligram as follows:

\[
\text{Micrograms of cefmenoxime per milligram} = \frac{T3R_u \times P_s \times 100 \times d}{R_s \times C_u (100 - L - S)}
\]

where:
- \(R_u\) = Area of the cefmenoxime peak in the chromatogram of the sample/Area of internal standard peak;
- \(R_s\) = Area of the cefmenoxime peak in the chromatogram of the cefmenoxime working standard/Area of internal standard peak;
- \(P_s\) = Cefmenoxime activity in the cefmenoxime working standard solution in micrograms per milliliter;
- \(C_u\) = Milligrams of sample per milliliter of sample solution;
- \(d\) = Dilution factor of the sample;
- \(L\) = Percent loss on drying (determined as directed in paragraph (b)(4) of this section); and
- \(S\) = Percent sodium carbonate (determined as directed in paragraph (b)(6) of this section).

(B) Milligrams of cefmenoxime per vial. Calculate the cefmenoxime content of the vial as follows:

\[
\text{Milligrams of cefmenoxime per vial} = \frac{R_v \times P_s \times d}{R_s \times 1,000}
\]

where:
- \(R_v\) = Area of the cefmenoxime peak in the chromatogram of the sample/Area of internal standard peak;
- \(R_s\) = Area of the cefmenoxime peak in the chromatogram of the cefmenoxime working standard/Area of internal standard peak;
- \(P_v\) = Cefmenoxime activity in the cefmenoxime working standard solution in micrograms per milliliter; and
- \(d\) = Dilution factor of the sample.
§ 442.225b Cephalothin sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephalothin sodium injection is a frozen aqueous solution of cephalothin sodium with one or more suitable and harmless buffer substances. It may contain sodium chloride or dextrose. Each milliliter contains cephalothin sodium equivalent to 20 milligrams, 40 milligrams, or 100 milligrams of cephalothin. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cephalothin that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 6.0 and not more than 8.5. The cephalothin sodium used conforms to the standards prescribed by §442.25a(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The cephalothin sodium used in making the batch for potency, loss on drying, pH, specific rotation, identity, and crystallinity.

(b) The batch for potency, sterility, pyrogens, and pH.

(ii) Samples required:

(a) The cephalothin sodium used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay. Thaw the ampoule contents as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) Potency. Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 microgram of cephalothin per milliliter (estimated).

(ii) Hydroxylamine colorimetric assay. Proceed as directed in §436.205 of this chapter, preparing the sample as follows: Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with distilled
§ 442.225c

Cephalothin sodium for injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephalothin sodium for injection is a dry mixture of cephalothin sodium with one or more suitable and harmless buffer substances. The cephalothin sodium may be isolated in the manufacture of cephalothin sodium for injection. Its cephalothin content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cephalothin that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 1.5 percent. When reconstituted as directed in the labeling, its pH is not less than 6.0 and not more than 8.5. If isolated, the cephalothin sodium used conforms to the standards prescribed by §442.25a(a)(1). If the cephalothin sodium is not isolated: The potency of the dry mixture is not less than 850 micrograms of cephalothin per milligram on an anhydrous basis when corrected for sodium bicarbonate; the specific rotation of the dry mixture in an aqueous solution containing 50 milligrams of cephalothin per milliliter at 25° C is +129° ±5°; and the dry mixture gives a positive identity test.

(2) Labeling. It shall be labeled in accordance with the requirements of §431.1 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) If isolated, the cephalothin sodium used in making the batch for potency, loss on drying, pH, specific rotation, identity, and crystallinity.

(b) The batch for potency, sterility, pyrogens, loss on drying, and pH. In addition, if the cephalothin sodium is not isolated, results of tests and assays on the dry mixture for potency, specific rotation, and identity.

(ii) Samples required:

(a) For all tests except sterility: A minimum of 10 immediate containers, unless the cephalothin sodium is not isolated, a minimum of 15 immediate containers.

(b) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Content; potency—(i) Sample preparation. Reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), for the microbiological agar diffusion assay or distilled water for the hydroxylamine colorimetric assay to obtain a stock solution of convenient concentration. In addition, if the cephalothin sodium is not isolated, dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), for the microbiological agar diffusion assay or distilled water for the hydroxylamine colorimetric assay to obtain a stock solution of convenient concentration. Correct the potency, micrograms of cephalothin per milligram, for sodium bicarbonate content determined as described in paragraph (b)(7) of this section.

(ii) Assay procedures. Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.
§ 442.230 Sterile cepapirin sodium.
The requirements for certification and the tests and methods of assay for sterile cepapirin sodium packaged for dispensing are described in § 442.29a.

§ 442.240 Cephradine injectable dosage forms.

§ 442.240a Cephradine for injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cephradine for injection is a dry mixture of cephradine and one or more suitable and harmless solubilizing and buffering agents. Its potency is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of cephalothin that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 5.0 percent. Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 8.0 and not more than 9.6. The cephradine used conforms to the standards prescribed by § 442.40a(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:
   (a) The sterile cephradine used in making the batch for potency, moisture, pH, cepalexin content, identity, and crystallinity.
   (b) The batch for potency, sterility, pyrogens, loss on drying, and pH.

(ii) Samples required:
   (a) The cephradine used in making the batch: 10 packages, each containing approximately 500 milligrams.
   (b) The batch:
      (1) For all tests except sterility: A minimum of 10 immediate containers.
      (2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Potency. Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) Microbiological agar diffusion assay. Proceed as directed in § 436.105 of this chapter.
chapter, preparing the sample for assay as follows: Reconstitute the sample as directed in the labeling for intramuscular use. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Further dilute an aliquot of this solution with solution 1 to the reference concentration of 10.0 micrograms of cephradine per milliliter (estimated).

(ii) Hydroxylamine colorimetric assay. Proceed as directed in §442.40(b)(1)(ii), preparing the sample as follows: Reconstitute the sample as directed in the labeling for intramuscular use. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Further dilute an aliquot of this solution with distilled water to 1 milligram of cephradine per milliliter (estimated).

(3) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(4) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 80 milligrams of cephradine per milliliter (estimated).

(5) Loss on drying. Proceed as directed in §436.200(b) of this chapter.

(6) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

§ 442.240b Sterile cephradine

The requirements for certification and the tests and methods of assay for sterile cephradine packaged for dispensing are described in §442.40a.

§ 442.250 Ceforanide for injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Ceforanide for injection is a dry mixture of ceforanide and L-lysine. Each milligram of ceforanide for injection contains not less than 900 micrograms and not more than 1,050 micrograms of ceforanide when corrected for L-lysine content. Its ceforanide content is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of ceforanide that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 3.0 percent. When reconstituted as directed in the labeling, its pH is not less than 5.5 and not more than 8.5. The ceforanide used conforms to the standards prescribed by §442.50a(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:
(a) The sterile ceforanide used in making the batch for ceforanide content, moisture, pH, and identity.
(b) The batch for ceforanide content, sterility, pyrogens, moisture, and pH.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:
(a) The ceforanide used in making the batch: 10 packages, each containing approximately 500 milligrams.
(b) The batch:
(1) For all tests except sterility: A minimum of 10 immediate containers.
(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) The batch:
(1) Ceforanide content. Determine both micrograms of ceforanide per milligram of sample and milligrams of ceforanide per container. Proceed as directed in §436.348 of this chapter, preparing the sample solution and calculating the ceforanide content as follows:

(i) Preparation of sample solution. Use separate containers for preparation of each sample solution as described in
paragraph (b)(1)(i) (a) and (b) of this section.

(a) Micrograms of ceforanide per milligram. Prepare a solution containing 1.0 milligrams per milliliter in mobile phase. Inject each sample within 5 minutes after dissolution.

(b) Milligrams of ceforanide per container. Reconstitute the sample with distilled water as directed in the labeling. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of ceforanide content in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with mobile phase to obtain a stock solution containing 10.0 milligrams per milliliter (estimated). Immediately dilute an aliquot of the stock solution with mobile phase to obtain a stock solution containing 10.0 milligrams per milliliter (estimated). Inject within 5 minutes, after preparation.

(ii) Calculations—(a) Micrograms of ceforanide per milligram. Calculate the micrograms of ceforanide per milligram of sample as follows:

\[
\text{Micrograms of ceforanide per milligram = } \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - L)}
\]

where:

- \(A_u\): Area of the ceforanide sample peak (at a retention time equal to that observed for the standard);
- \(A_s\): Area of the ceforanide peak in the chromatogram of the ceforanide working standard;
- \(P_s\): Ceforanide activity in the ceforanide working standard solution in micrograms per milliliter;
- \(C_u\): Milligrams of sample per milliliter of sample solution; and
- \(L\): Percent lysine content of the sample. (Determined as described in §436.349 of this chapter.)

(b) Milligrams of ceforanide per vial. Calculate the ceforanide content of the vial as follows:

\[
\text{Milligrams of ceforanide per vial} = \frac{A_u \times P_s \times d}{A_s \times 1,000}
\]

where:

- \(A_u\): Area of the ceforanide sample peak (at a retention time equal to that observed for the standard);
- \(A_s\): Area of the ceforanide peak in the chromatogram of the ceforanide working standard;
- \(P_s\): Ceforanide activity in the ceforanide working standard solution in micrograms per milliliter; and
- \(d\): Dilution factor of the sample.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except reconstitute the vials with approximately 3.0 milliliters of diluting fluid A per each gram of antibiotic activity. Transfer approximately 1 milliliter from each of 20 vials into a sterile 500-milliliter Erlenmeyer flask containing 200 milliliters of diluting fluid A. Filter as described in paragraph (e)(1)(ii) of this section, except in lieu of filtering with three 100-milliliter portions of diluting fluid A, rinse the filter membrane with three 100-milliliter portions of diluting fluid D followed by a final rinse with 100 milliliters of diluting fluid A.

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of ceforanide per milliliter.

(4) Moisture. Proceed as directed in §436.201 of this chapter.

(5) pH. Proceed as described in §436.202 of this chapter, using the solution obtained when the product is reconstituted as directed in the labeling.


§442.253 Cefotetan injectable dosage forms.

§442.253a Sterile cefotetan disodium.

The requirements for certification and the tests and methods of assay for
§ 442.253b Cefotetan sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefotetan sodium injection is a frozen, aqueous, iso-osmotic solution of cefotetan and sodium bicarbonate. It contains one or more suitable and harmless buffer substances and a tonicity adjusting agent. Each milliliter contains cefotetan disodium equivalent to 20 milligrams or 40 milligrams of cefotetan per milliliter. Its cefotetan content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefotetan that it is represented to contain. It is sterile. It contains not more than 0.17 endotoxin units per milligram of cefotetan. Its pH is not less than 4.0 and not more than 6.5. It passes the identity test. The cefotetan used conforms to the standards prescribed by § 442.52(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:
(A) The cefotetan used in making the batch for cefotetan potency, moisture, and identity.
(B) The batch for cefotetan potency, sterility, bacterial endotoxins, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:
(A) The cefotetan used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch:
(1) For all tests except sterility: A minimum of 12 immediate containers.
(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay. Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) Cefotetan potency. Proceed as directed in § 442.52(b)(1), except prepare the sample solution and calculate the cefotetan content as follows:

(i) Preparation of sample solution. Using a suitable hypodermic needle and syringe, remove an accurately measured portion from each container immediately after thawing and reaching room temperature and dilute with mobile phase to obtain a solution containing 200 micrograms of cefotetan per milliliter (estimated). Prepare the sample solution just prior to its introduction into the chromatograph.

(ii) Calculation. Calculate the milligrams of cefotetan per milliliter of sample as follows:

Micrograms of 

cefotetan per milligram = \frac{A_U \times P_S \times 100}{A_S \times C_U \times (100 - m)}

where:

A_U = Area of the cefotetan peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
A_S = Area of the cefotetan peak in the chromatogram of the cefotetan working standard;
P_S = Cefotetan activity in the cefotetan working standard solution in micrograms per milliliter;
C_U = Milligrams of sample per milliliter of sample solution; and
m = Percent moisture content of the sample.

(2) Sterility. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Bacterial endotoxins. Proceed as directed in the U.S. Pharmacopeia bacterial endotoxins test.

(4) pH. Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

(5) Identity. The high-performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cefotetan working standard.

§ 442.253a sterile cefotetan disodium packaged for dispensing are described in § 442.53a.

§ 442.255b Ceftriaxone sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Ceftriaxone sodium injection is a frozen aqueous iso-osmotic solution of ceftriaxone sodium which may contain one or more suitable and harmless buffer substances. Each milliliter contains ceftriaxone sodium equivalent to 10, 20, or 40 milligrams of ceftriaxone per milliliter. Its ceftriaxone content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of ceftriaxone that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 6.0 and not more than 8.0. It passes the identity test. The ceftriaxone sodium used conforms to the standards prescribed by §442.55(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.5 of this chapter, each such request shall contain:

(i) Results of tests and assays on:
(A) The ceftriaxone sodium used in making the batch for potency, moisture, pH, crystallinity, and identity.
(B) The batch for content, sterility, pyrogens, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:
(A) The ceftriaxone sodium used in making the batch: 10 packages, each containing 500 milligrams.
(B) The batch:
(1) For all tests except sterility: A minimum of 10 immediate containers.
(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay. Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) Ceftriaxone content. Proceed as directed in §442.55a(b)(1) of this chapter, except prepare the sample solution and calculate the ceftriaxone content as follows:

(i) Preparation of sample solution. Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container immediately after thawing and reaching room temperature and dilute with mobile phase to obtain a solution containing 380 micrograms of ceftriaxone per milliliter (estimated). Prepare the sample solution just prior to its introduction into the chromatograph.

(ii) Calculation. Calculate the milligrams of ceftriaxone anhydrous free acid per milliliter of sample as follows:

\[
\text{Milligrams of ceftriaxone anhydrous free acid} = \frac{A_u \times P_s \times d}{A_s \times 1,000}
\]

where:

- \(A_u\) = Area of the ceftriaxone peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \(A_s\) = Area of the ceftriaxone peak in the chromatogram of the ceftriaxone working standard;
- \(P_s\) = Ceftriaxone activity in the ceftriaxone working standard solution in micrograms of anhydrous free acid per milliliter; and
- \(d\) = Dilution factor of the sample.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) Pyrogens. Proceed as directed in §436.32(a) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 40 milligrams of ceftriaxone per kilogram.

(4) pH. Proceed as directed in §436.202 of this chapter, using the undiluted solution.

(5) Identify. The high-performance liquid chromatogram of the sample determined as directed in paragraph...
§ 442.258 Cefotiam dihydrochloride for injection

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefotiam dehydrochloride for injection is a dry mixture of cefotiam dihydrochloride and sodium carbonate. Its cefotiam potency is satisfactory if each milligram of cefotiam dihydrochloride for injection contains not less than 790 micrograms and not more than 925 micrograms of cefotiam on an anhydrous basis, when corrected for sodium carbonate content. Its cefotiam content is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefotiam that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 6.0 percent. The pH of an aqueous solution containing 100 milligrams per milliliter is not less than 5.7 and not more than 7.2. The cefotiam dihydrochloride used conforms to the standards prescribed by § 442.58a(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The cefotiam dihydrochloride used in making the batch for potency, moisture, identity, and crystallinity.

(B) The batch for cefotiam potency, cefotiam content, sterility, pyrogens, loss on drying, pH, and sodium carbonate content.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The cefotiam dihydrochloride used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Cefotiam potency and content. Determine both micrograms of cefotiam per milligram of sample and milligrams of cefotiam per container. Proceed as directed in § 442.58a(b)(1), preparing the sample solutions and calculating the potency and content as follows:

(i) Preparation of sample solutions. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(i) (A) and (B) of this section.

(A) Cefotiam potency (micrograms of cefotiam per milligram). Dissolve an accurately weighed sample with sufficient distilled water to obtain a solution containing approximately 1,000 micrograms of cefotiam per milliliter. Further dilute this solution with mobile phase to obtain a solution containing approximately 1,000 micrograms of cefotiam per milliliter.

(B) Cefotiam content (milligrams of cefotiam per vial). Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute the solution thus obtained with sufficient distilled water to obtain a solution containing 1,000 micrograms of cefotiam activity per milliliter (estimated).

Further dilute this solution with mobile phase to obtain a solution containing 50 micrograms of cefotiam activity per milliliter (estimated).

(B) Cefotiam content (milligrams of cefotiam per vial). Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute the solution thus obtained with sufficient distilled water to obtain a solution containing 1,000 micrograms of cefotiam activity per milliliter (estimated).

(ii) Calculations—(A) Cefotiam potency (micrograms per milligram). Calculate the micrograms of cefotiam per milligram as follows:
§ 442.260 Cefpiramide sodium for injection.

(a) Requirements for certification—

(1) Standards of identity, strength, quality, and purity. Cefpiramide sodium for injection is a dry mixture of cefpiramide and sodium benzoate. It contains other buffers and preservatives. Its cefpiramide potency is satisfactory if each milligram of cefpiramide sodium for injection contains not less than 754 micrograms and not more than 924 micrograms of cefpiramide on an anhydrous basis. Its cefpiramide content is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefpiramide that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 3.0 percent. Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 6.0 and not more than 8.0. It passes the identity test. The cefpiramide used conforms to the standards prescribed by §442.60(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The cefpiramide used in making the batch for potency, moisture, pH, total related substances, specific rotation, identity, and crystallinity.

(B) The batch for cefpiramide potency, cefpiramide content, sterility, pyrogens, moisture, pH, and identity.

(ii) Samples, if required by the Center for Drug Evaluation and Research:

(A) The cefpiramide used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—

(1) Cefpiramide potency and content. Determine both micrograms of cefpiramide per milligram of sample and milligrams of cefpiramide per container.

Micrograms of cefotiam per milligram

\[ \text{Micrograms of cefotiam per milligram} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - L - S)} \]

where:

- \( A_u \) = Area of the cefotiam peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \( A_s \) = Area of the cefotiam peak in the chromatogram of the cefotiam working standard;
- \( P_s \) = Cefotiam activity in the cefotiam working standard solution in micrograms per milliliter;
- \( C_u \) = Milligrams of the sample per milliliter of sample solution;
- \( L \) = Percent loss on drying (determined as directed in paragraph (b)(4) of this section); and
- \( S \) = Percent sodium carbonate (determined as directed in paragraph (b)(6) of this section).

(B) Cefotiam content (milligrams of cefotiam per vial). Calculate the cefotiam content of the vial as follows:

Milligrams of cefotiam per vial

\[ \text{Milligrams of cefotiam per vial} = \frac{A_u \times P_s \times d}{A_s \times 1,000} \]

where:

- \( A_u \) = Area of the cefotiam peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- \( A_s \) = Area of the cefotiam peak in the chromatogram of the cefotiam working standard;
- \( P_s \) = Cefotiam activity in the cefotiam working standard solution in micrograms per milliliter; and
- \( d \) = Dilution factor of the sample.
Proceed as directed in §442.60(b)(1), preparing the sample solutions and calculating the potency and content as follows:

(i) Preparation of sample solutions. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(i)(A) and (b)(1)(i)(B) of this section.

(A) Cefpiramide potency (micrograms of cefpiramide per milligram). Dissolve an accurately weighed sample with sufficient mobile phase to obtain a solution containing approximately 0.25 milligram of cefpiramide per milliliter (estimated).

(B) Cefpiramide content (milligrams of cefpiramide per vial). Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute the solution thus obtained with sufficient distilled water to obtain a solution containing 1.0 milligram of cefpiramide activity per milliliter (estimated). Further dilute this solution with mobile phase to obtain a solution containing 0.25 milligram of cefpiramide activity per milliliter (estimated).

(ii) Calculations—(A) Cefpiramide potency (micrograms per milligram). Calculate the micrograms of cefpiramide per milligram as follows:

$$\text{Micrograms of cefpiramide per milligram} = \frac{A_u \times P_s \times d}{A_s \times C_u \times (100 - m)}$$

where:

- $A_u$ = Area of the cefpiramide peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- $A_s$ = Area of the cefpiramide peak in the chromatogram of the cefpiramide working standard;
- $P_s$ = Cefpiramide activity in the cefpiramide working standard solution in micrograms per milliliter;
- $C_u$ = Milligrams of the sample per milliliter of sample solution;
- $m$ = Percent moisture content of the sample.

(B) Cefpiramide content (milligrams of cefpiramide per vial). Calculate the cefpiramide content of the vial as follows:

$$\text{Milligrams of cefpiramide per vial} = \frac{A_u \times P_s \times d}{A_s \times 1.000}$$

where:

- $A_u$ = Area of the cefpiramide peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);
- $A_s$ = Area of the cefpiramide peak in the chromatogram of the cefpiramide working standard;
- $P_s$ = Cefpiramide activity in the cefpiramide working standard solution in micrograms per milliliter; and
- $d$ = Dilution factor of the sample.

(2) Sterility. Proceed as directed in §436.20 of this chapter, using the method described in §436.20(e)(1).

(3) Pyrogens. Proceed as directed in §436.32(b) of this chapter, using a solution containing 50 milligrams of cefpiramide per milliliter.

(4) Moisture. Proceed as directed in §436.201 of this chapter.

(5) pH. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(6) Identify. The high-performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cefpiramide working standard.

[$55 FR 14242, Apr. 17, 1990$]

§ 442.270 Cefmetazole injectable dosage forms.

§ 442.270a Sterile cefmetazole sodium.

The requirements for certification and the tests and methods of assay for sterile cefmetazole sodium packaged for dispensing are described in §442.70a.

[$55 FR 6636, Feb. 26, 1990$]

§ 442.270b Cefmetazole sodium injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Cefmetazole sodium injection is a frozen, aqueous, iso-osmotic solution of cefmetazole and sodium citrate. It contains one or more suitable
Food and Drug Administration, HHS

and harmless buffer substances and a
tonicity adjusting agent. Each milli-
liter contains cefmetazole sodium
equivalent to 20 milligrams or 40 milli-
grams of cefmetazole per milliliter. Its
cefmetazole content is satisfactory if it
is not less than 90 percent and not
more than 120 percent of the number of
milligrams of cefmetazole that it is
represented to contain. It is sterile. It
contains not more than 0.2 endotoxin
units per milligram. Its pH is not less
than 4.2 and not more than 6.2. It
passed the identity test. The
cefmetazole used conforms to the
standards prescribed by § 442.69(a)(1).

(2) Labeling. It shall be labeled in ac-
cordance with the requirements of
§ 432.5 of this chapter.

(3) Requests for certification; samples.
In addition to complying with the re-
quirements of § 431.1 of this chapter,
each such request shall contain:
(i) Results of tests and assays on:
(A) The cefmetazole used in making
the batch for potency, moisture, and
identity.
(B) The batch for potency, sterility,
bacterial endotoxins, pH, and identity.
(ii) Samples, if required by the Direc-
tor, Center for Drug Evaluation and
Research:
(A) The cefmetazole used in making
the batch: 10 packages, each containing
approximately 500 milligrams.
(B) The batch:
(1) For all tests except sterility: A
minimum of 12 immediate containers.
(2) For sterility testing: 20 immediate
containers, collected at regular inter-
vals throughout each filling operation.
(b) Tests and methods of assay. Thaw
the sample as directed in the labeling.
The sample solution used for testing
must be at room temperature.

(1) Cefmetazole potency. Proceed as di-
rected in § 442.70(a)(b)(1), except prepare
the sample solution and calculate the
cefmetazole content as follows:
(i) Preparation of sample solution.
Using a suitable hypodermic needle and
syringe, remove an accurately meas-
ured portion from each container im-
mEDIATELY after thawing and reaching
room temperature and dilute with mo-
ible phase to obtain a solution contain-
ing 500 micrograms of cefmetazole per
milliliter (estimated). Prepare the
sample solution just prior to its intro-
duction into the chromatograph.
(ii) Calculation. Calculate the milli-
grams of cefmetazole per milliliter of
sample as follows:

\[
\text{Milligrams of cefmetazole per milliliter} = \frac{A_U \times P_S \times d}{A_S \times 1,000}
\]

where:
\( A_U \) = Area of the cefmetazole peak in the chro-

matogram of the ± sample (at a retention
time equal to that observed for the
standard);
\( A_S \) = Area of the cefmetazole peak in the chro-

matogram of the cefmetazole working
standard;
\( P_S \) = Cefmetazole activity in the cefmetazole
working standard solution in
micrograms per milliliter; and
\( d \) = Dilution factor of the sample.

(2) Sterility. Proceed as directed in
§ 436.20 of this chapter, using the meth-
od described in paragraph (e)(1) of that
section.

(3) Bacterial endotoxins. Proceed as di-
rected in the United States Pharma-
copeia bacterial endotoxins test.

(4) pH. Proceed as directed in § 436.202
of this chapter, using the undiluted so-
lution.

(5) Identity. The high-performance
liquid chromatogram of the sample de-
termined as directed in paragraph
(b)(1) of this section compares quali-
atively to that of the cefmetazole
working standard.

[59 FR 12546, Mar. 17, 1994]

PART 443—CARBACEPHEN
ANTIBIOTIC DRUGS

Subpart A—Bulk Drugs

Sec.
443.20 Loracarbef.

Subpart B—Oral Dosage Forms

443.120 Loracarbef oral dosage forms.
443.120a Loracarbef capsules.
443.120b Loracarbef for oral suspension.

Authority: Sec. 507 of the Federal Food,

Source: 58 FR 26667, May 4, 1993, unless
otherwise noted.